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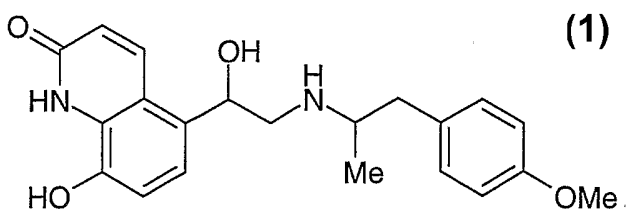
(54) Title: MEDICAMENTS FOR INHALATION COMPRISING ANTICHOLINERGICS AND A BETAMIMETIC

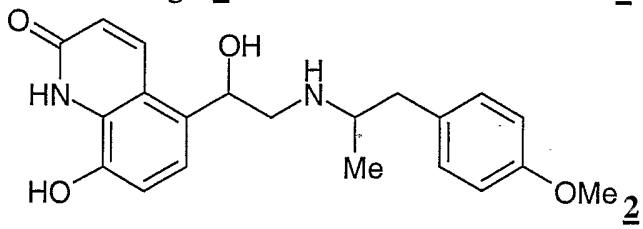


(1)

(57) Abstract: The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one anticholinergic 1 and a betamimetic of formula 2 processes for preparing them and their use in the treatment of respiratory complaints.

MEDICAMENTS FOR INHALATION COMPRISING ANTICHOLINERGICS AND A BETAMIMETIC

The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one anticholinergic **1** and a betamimetic of formula **2**



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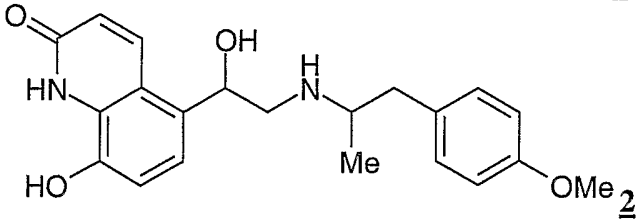
processes for preparing them and their use in the treatment of respiratory complaints.

Description of the invention

The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one anticholinergic **1** and a betamimetic of formula **2**



2

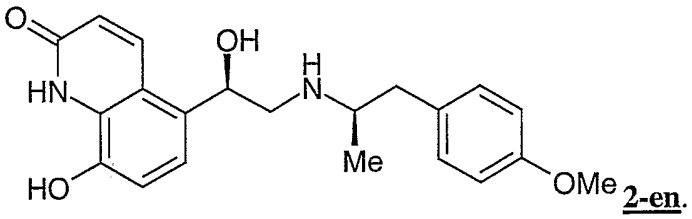
optionally in the form of its diasteromers, mixtures of its diasteromers, racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof, and optionally together with a pharmaceutically acceptable excipient.

Examples of pharmacologically acceptable acid addition salts of the betamimetic **2** according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts of **2**.

According to the invention, the salts of **2** selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate, maleate and xinafoate are preferred. Particularly preferred is the hydrochloric acid salt of **2** .

In the pharmaceutical compositions according to the invention, the compound **2** may be present in the form of its racemates, enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.) If the compounds **2** are used in the form of their enantiomers, it is particularly preferable to use the enantiomers possessing R-configuration at the C-OH group.

Of particular interest within the scope of the instant invention is the R,R-enantiomer of formula **2-en**



2-en.

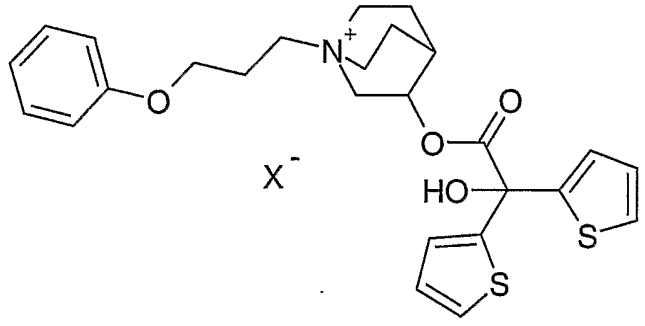
Within the scope of the present invention the betamimetic **2** may possibly also be referred to as sympathomimetic or beta$_2$-agonist (β_2-agonist). All these terms are to be regarded as interchangeable for the purposes of the present invention.

Within the scope of the present invention the anticholinergic agents **1** are in a preferred embodiment salts selected from among tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts and trospium salts. In the above-mentioned salts the cations tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium and trospium are the pharmacologically active components. Within the scope of the present patent application, an explicit reference to the above cations is indicated by the use of the number **1'**. Any reference to the aforementioned salts **1** naturally also includes a reference to the ingredients **1'** (tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium or trospium). By the salts **1** which may be used within the scope of the present invention are meant the compounds which contain, in addition to tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium or trospium as counter-ion (anion), chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, wherein chloride, bromide, iodide, sulphate, methanesulphonate or para-toluenesulphonate are preferred. Within the scope of the present invention, the methanesulphonate, chloride, bromide and iodide are preferred of all the salts **1**. If trospium salts are used the chloride is of particular

importance. From the other salts mentioned hereonbefore the methanesulphonate and bromide are of particular importance. Of particular importance according to the invention are salts **1** selected from among tiotropium salts, oxitropium salts and ipratropium salts. Of outstanding importance according to the invention are salts **1** selected from among tiotropium bromide, oxitropium bromide and ipratropium bromide. Tiotropium bromide is particularly preferred. The aforementioned salts may be optionally present in form of their solvates or hydrates, preferably in form of their hydrates. If tiotropium bromide is used it is preferably present in form of its crystalline tiotropium bromide monohydrate as disclosed in WO 02/30928. In case tiotropium bromid is used in anhydrous form, it is preferably present in form of the crystalline tiotropium bromide anhydrate disclosed in WO 03/000265.

Optionally the anticholinergic agents mentioned hereinbefore possess chiral carbon centers. In this case the pharmaceutical combinations according to the invention may contain the anticholinergic agents in form of their enantiomers, mixtures of enantiomers or racemats. Preferably chiral anticholinergics are present in form of one of their pure enantiomers.

Within the scope of the present invention the anticholinergic agents **1** are in another preferred embodiment selected from the salts of LAS 34273, being characterized by the formula **1a**



1a

wherein

X⁻ denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

Preferably, the salts of formula **1a** are used wherein

X^- denotes an anion with a single negative charge selected from among the fluoride, chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

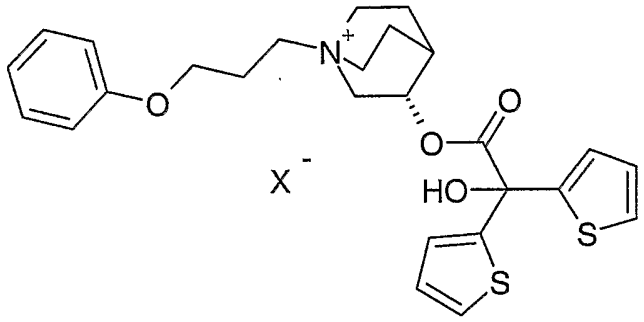
Most preferably, the salts of formula **1a** are used wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

Particularly preferred according to the invention is the salt of formula **1a** wherein X^- denotes bromide.

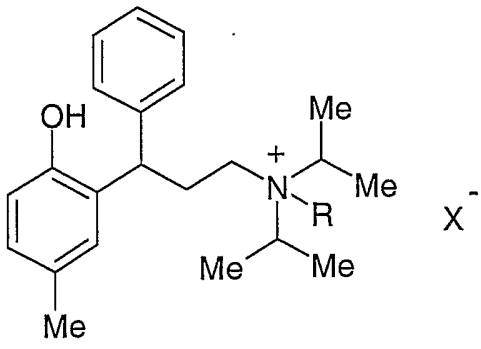
Of particular interest according to the invention are the enantiomers of formula **1a-en**



1a-en

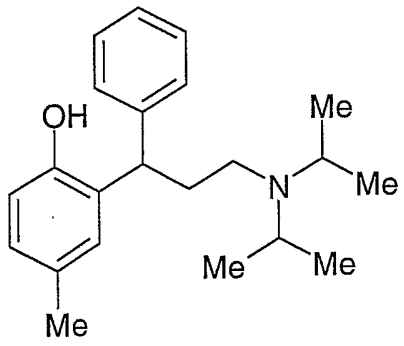
wherein X^- may have the meanings as mentioned hereinbefore.

In a yet another preferred embodiment according to the invention the anticholinergic agents **1** are represented by the compounds of formula **1b**



1b

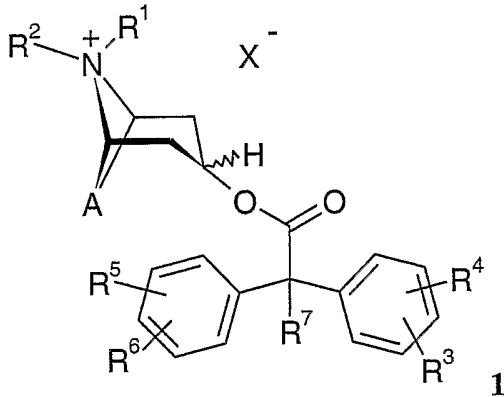
wherein R is either methyl or ethyl and wherein X^- may have the meanings as mentioned hereinbefore. In the alternative the compound according to formula **1b** may be present in form of its free base according to formula **1b-base**



1b-base.

The pharmaceutical combinations according to the invention may contain the anticholinergic agent of formula **1b** (or **1b-base**) in form of their enantiomers, mixtures of enantiomers or racemats. Preferably, the anticholinergic agent of formula **1b** (or **1b-base**) is present in form of its R-enantiomer.

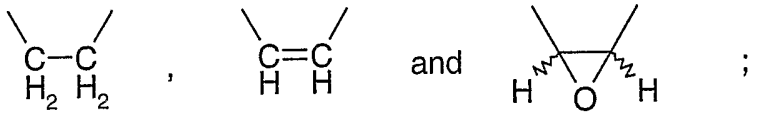
Within the scope of the present invention the anticholinergic agents **1** are in a yet another preferred embodiment selected from the compounds of formula **1c**



1c

wherein

A denotes a double-bonded group selected from among



;

X^- may have the meanings as mentioned hereinbefore, preferably chloride, bromide or methansulphonate,

R^1 and R^2 which may be identical or different denote a group selected from among

methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

R^3, R^4, R^5 and R^6, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2;

R^7 denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, $-CH_2-F$, $-CH_2-CH_2-F$, $-O-CH_2-F$, $-O-CH_2-CH_2-F$, $-CH_2-OH$, $-CH_2-CH_2-OH$, CF_3, $-CH_2-OMe$, $-CH_2-CH_2-OMe$, $-CH_2-OEt$, $-CH_2-CH_2-OEt$, -O-COMe, -O-COEt, $-O-COCF_3$, $-O-COCF_3$, fluorine, chlorine or bromine.

The compounds of formula **1c** are known in the art (WO 02/32899).

Preferred compounds of formula **1c** within the combinations according to the invention are those, wherein

X^- denotes bromide;

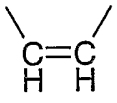
R^1 and R^2 which may be identical or different denote a group selected from methyl and ethyl, preferably methyl;

R^3, R^4, R^5 and R^6, which may be identical or different, denote hydrogen, methyl, methyloxy, chlorine or fluorine;

R^7 denotes hydrogen, methyl or fluorine.

Of particular importance within the combinations according to the invention are compounds of general formula **1c**, wherein

A denotes a double-bonded group selected from among



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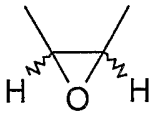


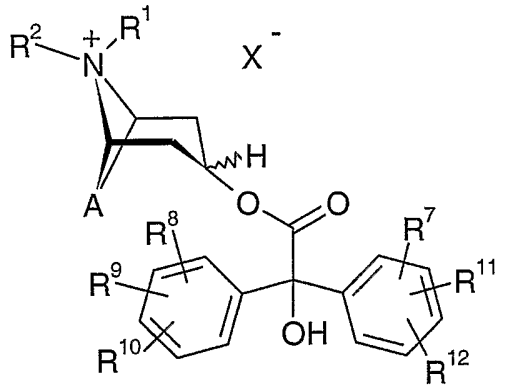
The compounds of formula **1c**, may optionally be present in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

Of particular importance are those pharmaceutical compositions that contain the compound of formula **2** in combination with one of the following compounds **1c**:

- tropenol 2,2-diphenylpropionic acid ester methobromide,
- scopine 2,2-diphenylpropionic acid ester methobromide,
- scopine 2-fluoro-2,2-diphenylacetic acid ester methobromide and

- tropenol 2-fluoro-2,2-diphenylacetic acid ester methobromide.

Within the scope of the present invention the anticholinergic agents **1** are in a yet another preferred embodiment selected from the compounds of formula **1d**



1d

wherein

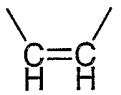
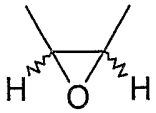
A, X^-, R^1 and R^2 may have the meanings as mentioned hereinbefore and wherein

R^7, R^8, R^9, R^{10}, R^{11} and R^{12}, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2, with the proviso that at least one of the groups R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is not hydrogen.

The compounds of formula **1d** are known in the art (WO 02/32898).

Particularly preferred within the combinations according to the invention are compounds of general formula **1d**, wherein

A denotes a double-bonded group selected from among

 and  ;

X^- denotes bromide;

R^1 and R^2 which may be identical or different denote methyl or ethyl, preferably methyl;

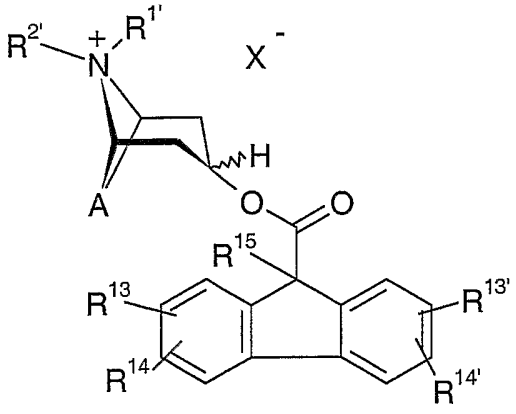
R^7, R^8, R^9, R^{10}, R^{11} and R^{12}, which may be identical or different, denote hydrogen, fluorine, chlorine or bromine, preferably fluorine with the proviso that at least one of the groups R^7, R^8, R^9, R^{10}, R^{11} and R^{12} not hydrogen.

Of particular importance are those pharmaceutical compositions that contain the compound of formula **2** in combination with one of the following compounds **1d**:

- tropenol 3,3',4,4'-tetrafluorobenzilic acid ester methobromide,
- scopine 3,3',4,4'-tetrafluorobenzilic acid ester methobromide,
- scopine 4,4'-difluorobenzilic acid ester methobromide,
- tropenol 4,4'-difluorobenzilic acid ester methobromide,
- scopine 3,3'-difluorobenzilic acid ester methobromide, and
- tropenol 3,3'-difluorobenzilic acid ester methobromide.

The pharmaceutical compositions according to the invention may contain the compounds of formula **1d** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

Within the scope of the present invention the anticholinergic agents **1** are in a yet another preferred embodiment selected from the compounds of formula **1e**



1e

wherein A and X^- may have the meanings as mentioned hereinbefore, and wherein

R^{15} denotes hydrogen, hydroxy, methyl, ethyl, $-CF_3$, CHF_2 or fluorine;

$R^{1'}$ and $R^{2'}$ which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen,

or

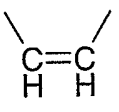
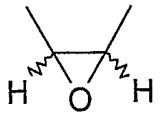
$R^{1'}$ and $R^{2'}$ together denote a $-C_3$-C_5-alkylene-bridge;

R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen.

The compounds of formula **1e** are not yet known in the art.

Particularly preferred within the combinations according to the invention are compounds of general formula **1e**, wherein

A denotes a double-bonded group selected from among

 and  ;

X^- denotes an anion selected from among chloride, bromide and methanesulphonate, preferably bromide;

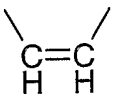
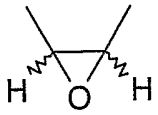
R^{15} denotes hydroxy, methyl or fluorine, preferably methyl or hydroxy;

$R^{1'}$ and $R^{2'}$ which may be identical or different represent methyl or ethyl, preferably methyl;

R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$ which may be identical or different represent hydrogen, $-CF_3$, $-CHF_2$ or fluorine, preferably hydrogen or fluorine.

Particularly preferred within the combinations according to the invention are compounds of general formula **1e**, wherein

A denotes a double-bonded group selected from among

 and  ;

X^- denotes bromide;

R^{15} denotes hydroxy or methyl, preferably methyl;

$R^{1'}$ and $R^{2'}$ which may be identical or different represent methyl or ethyl, preferably methyl;

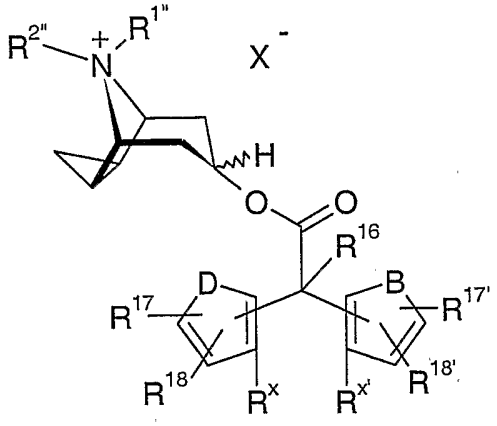
R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$ which may be identical or different represent hydrogen or fluorine.

Of particular importance are those pharmaceutical compositions that contain the compound of formula **2** in combination with one of the following compounds **1e**:

- tropenol 9-hydroxy-fluorene-9-carboxylate methobromide ;
- tropenol 9-fluoro-fluorene-9-carboxylate methobromide ;
- scopine 9-hydroxy-fluorene-9-carboxylate methobromide ;
- scopine 9-fluoro-fluorene-9-carboxylate methobromide ;
- tropenol 9-methyl-fluorene-9-carboxylate methobromide ;
- scopine 9-methyl-fluorene-9-carboxylate methobromide .

The pharmaceutical compositions according to the invention may contain the compounds of formula **1e** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

Within the scope of the present invention the anticholinergic agents **1** are in a yet another preferred embodiment selected from the compounds of formula **1f**



1f

wherein X^- may have the meanings as mentioned hereinbefore, and wherein

D and B which may be identical or different, preferably identical, denote -O, -S, -NH, $-CH_2$, -CH=CH, or $-N(C_1\text{-}C_4\text{-alkyl})$-;

R^{16} denotes hydrogen, hydroxy, $-C_1\text{-}C_4$-alkyl, $-C_1\text{-}C_4$-alkyloxy, $-C_1\text{-}C_4$-alkylene-Halogen, $-O\text{-}C_1\text{-}C_4$-alkylene-halogen, $-C_1\text{-}C_4$-alkylene-OH, $-CF_3$, CHF_2, $-C_1\text{-}C_4$-alkylene-$C_1\text{-}C_4$-alkyloxy, $-O\text{-}COC_1\text{-}C_4$-alkyl, $-O\text{-}COC_1\text{-}C_4$-alkylene-halogen, $-C_1\text{-}C_4$-alkylene-$C_3\text{-}C_6$-cycloalkyl, $-O\text{-}COCF_3$ or halogen;

$R^{1"}$ and $R^{2"}$ which may be identical or different, denote $-C_1\text{-}C_5$-alkyl, which may optionally be substituted by $-C_3\text{-}C_6$-cycloalkyl, hydroxy or halogen,

or

$R^{1"}$ and $R^{2"}$ together denote a $-C_3\text{-}C_5$-alkylene bridge;

R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$, which may be identical or different, denote hydrogen, $C_1\text{-}C_4$-alkyl, $C_1\text{-}C_4$-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, $C_1\text{-}C_4$-alkyl, $C_1\text{-}C_4$-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen

or

R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH, $-CH_2$, $-CH_2\text{-}CH_2$-, $-N(C_1\text{-}C_4\text{-alkyl})$, $-CH(C_1\text{-}C_4\text{-alkyl})$- and $-C(C_1\text{-}C_4\text{-alkyl})_2$.

The compounds of formula **1f** are not yet known in the art.

Particularly preferred within the combinations according to the invention are compounds of general formula **1f** wherein

X^- denotes chloride, bromide, or methanesulphonate, preferably bromide;

D and B which may be identical or different, preferably identical, denote -O, -S, -NH or -CH=CH-;

R^{16} denotes hydrogen, hydroxy, -C_1-C_4-alkyl, -C_1-C_4-alkyloxy, $-CF_3$, $-CHF_2$, fluorine, chlorine or bromine;

$R^{1"}$ and $R^{2"}$ which may be identical or different, denote C_1-C_4-alkyl, which may optionally be substituted by hydroxy, fluorine, chlorine or bromine,
or
$R^{1"}$ and $R^{2"}$ together denote a -C_3-C_4-alkylene-bridge;

R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$, which may be identical or different, denote hydrogen, C1-C4-alkyl, C1-C4-alkyloxy, hydroxy, -CF3, -CHF2, CN, NO2, fluorine, chlorine or bromine;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2, fluorine, chlorine or bromine
or
R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH- and $-CH_2-$.

Particularly preferred within the combinations according to the invention are compounds of general formula **1f**, wherein

X^- denotes chloride, bromide, or methanesulphonate, preferably bromide;

D and B which may be identical or different, preferably identical, denote -S or -CH=CH-;

R^{16} denotes hydrogen, hydroxy or methyl;

$R^{1"}$ and $R^{2"}$ which may be identical or different, denote methyl or ethyl;

R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$, which may be identical or different, denote hydrogen, $-CF_3$ or fluorine, preferably hydrogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, $-CF_3$ or fluorine, preferably hydrogen or

R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

Particularly preferred within the combinations according to the invention are compounds of general formula **1f,** wherein

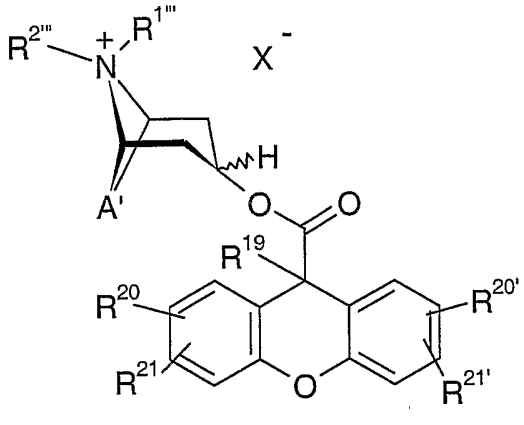
X^- denotes bromide;
D and B denote -CH=CH-;
R^{16} denotes hydrogen, hydroxy or methyl;
$R^{1''}$ and $R^{2''}$ denote methyl;
R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$, which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;
R^X and $R^{X'}$ which may be identical or different, denote hydrogen or fluorine, preferably hydrogen or
R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

Of particular importance are those pharmaceutical compositions that contain the compound of formula **2** in combination with one of the following compounds **1f**:

- cyclopropyltropine benzilate methobromide;
- cyclopropyltropine 2,2-diphenylpropionate methobromide;
- cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide ;
- cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.

The pharmaceutical compositions according to the invention may contain the compounds of formula **1f** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

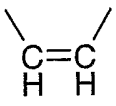
Within the scope of the present invention the anticholinergic agents **1** are in a yet another preferred embodiment selected from the compounds of formula **1g**



1g

wherein X^- may have the meanings as mentioned hereinbefore, and wherein

A' denotes a double-bonded group selected from among

 and  ;

R^{19} denotes hydroxy, methyl, hydroxymethyl, ethyl, $-CF_3$, CHF_2 or fluorine;

$R^{1'''}$ and $R^{2'''}$ which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen,

or

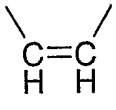
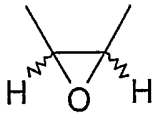
$R^{1'''}$ and $R^{2'''}$ together denote a $-C_3$-C_5-alkylene-bridge;

R^{20}, R^{21}, $R^{20'}$ and $R^{21'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen.

The compounds of formula **1g** are not yet known in the art.

Particularly preferred within the combinations according to the invention are compounds of general formula **1g** wherein

A' denotes a double-bonded group selected from among

 and  ;

X^- denotes chloride, bromide or methanesulphonate, preferably bromide;

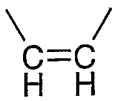
R^{19} denotes hydroxy or methyl;

$R^{1'''}$ and $R^{2'''}$ which may be identical or different represent methyl or ethyl, preferably methyl;

R^{20}, R^{21}, $R^{20'}$ and $R^{21'}$ which may be identical or different represent hydrogen, $-CF_3$, $-CHF_2$ or fluorine, preferably hydrogen or fluorine.

Particularly preferred within the combinations according to the invention are compounds of general formula **1g** wherein

A' denotes a double-bonded group selected from among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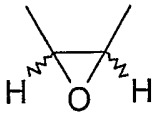

;

X^- denotes bromide;

R^{19} denotes hydroxy or methyl, preferably methyl;

$R^{1'''}$ and $R^{2'''}$ which may be identical or different represent methyl or ethyl, preferably methyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different represent hydrogen or fluorine.

Of particular importance are those pharmaceutical compositions that contain the compound of formula **2** in combination with one of the following compounds **1g**:

- tropenol 9-hydroxy-xanthene-9-carboxylate methobromide ;
- scopine 9-hydroxy-xanthene-9-carboxylate methobromide ;
- tropenol 9-methyl-xanthene-9-carboxylate methobromide ;
- scopine 9-methyl-xanthene-9-carboxylate methobromide ;
- tropenol 9-ethyl-xanthene-9-carboxylate methobromide ;
- tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide ;
- scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide .

The pharmaceutical compositions according to the invention may contain the compounds of formula **1g** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 5 carbon atoms. Examples include: methyl, ethyl, propyl or butyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Prop or Bu. Unless otherwise stated, the definitions propyl and butyl also include all

possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec. butyl and tert.-butyl, etc.

The cycloalkyl groups used, unless otherwise stated, are alicyclic groups with 3 to 6 carbon atoms. These are the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. According to the invention cyclopropyl is of particular importance within the scope of the present invention.

The alkylene groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 5 carbon atoms. Examples include: methylene, ethylene, propylene or butylene.

The alkylene-halogen groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably disubstituted, by a halogen. Accordingly, unless otherwise stated, the term alkylene-OH groups denotes branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by a hydroxy.

The alkyloxy groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 5 carbon atoms which are linked via an oxygen atom. The following may be mentioned, for example: methyloxy, ethyloxy, propyloxy or butyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to by the abbreviations MeO, EtO, PropO or BuO. Unless otherwise stated, the definitions propyloxy and butyloxy also include all possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and iso-propyloxy, butyloxy includes iso-butyloxy, sec. butyloxy and tert.-butyloxy, etc. The word alkoxy may also possibly be used within the scope of the present invention instead of the word alkyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to as methoxy, ethoxy, propoxy or butoxy.

The alkylene-alkyloxy groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 5 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by an alkyloxy group.

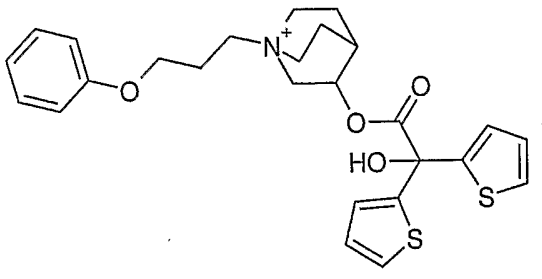
The -O-CO-alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 4 carbon atoms which are bonded via an ester group. The alkyl groups are bonded directly to the carbonylcarbon of the ester group. The term -O-CO-alkyl-halogen group should be understood analogously. The group -O-CO-CF_3 denotes trifluoroacetate.

Within the scope of the present invention halogen denotes fluorine, chlorine, bromine or iodine. Unless otherwise stated, fluorine and bromine are the preferred halogens. The group CO denotes a carbonyl group.

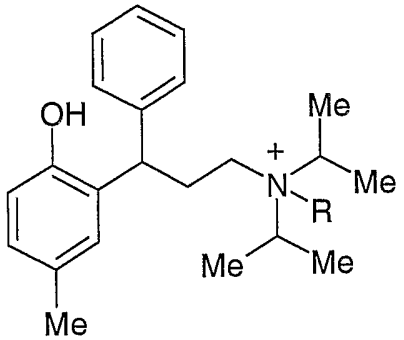
Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if an anticholinergic **1** is used with the betamimetic of formula **2**.

The beneficial therapeutic effect mentioned above may be observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate formulations. According to the invention, it is preferable to administer the two active substance ingredients simultaneously in a single formulation.

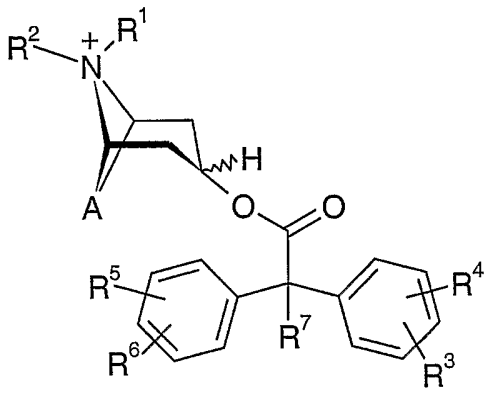
Within the scope of the present invention, any reference to the compounds **1'** is to be regarded as a reference to the pharmacologically active cations contained in the salts **1**. These are the cations tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium, trospium or the cations of the following formulae



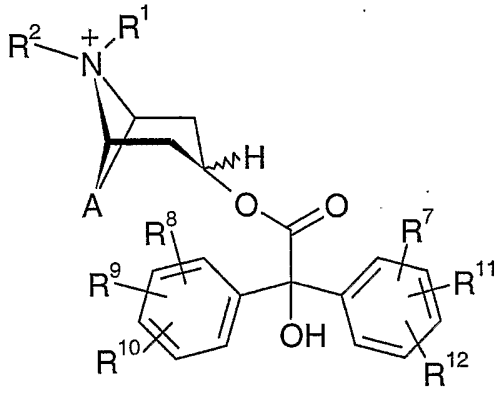
1a';



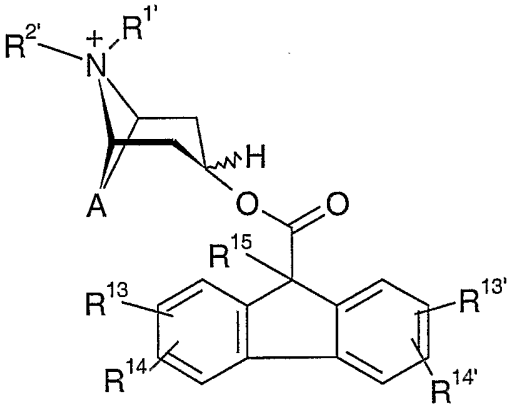
1b';



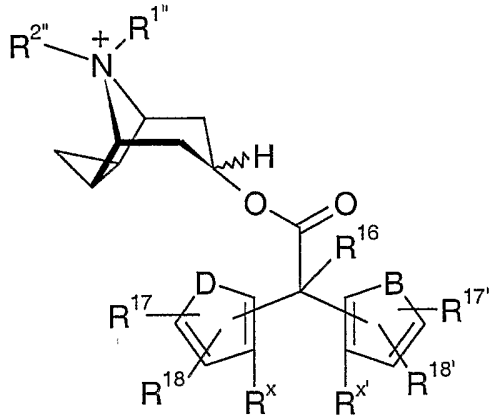
1c;



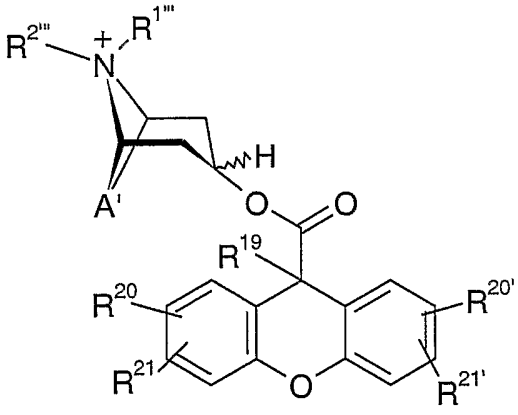
1d'



1e';



1f';



or 1g'.

In the pharmaceutical combinations mentioned above the active substances may be combined in a single preparation or contained in two separate formulations. Pharmaceutical compositions which contain the active substances 1 and 2 in a single preparation are preferred according to the invention.

In one aspect the present invention relates to the abovementioned pharmaceutical compositions which contain, in addition to therapeutically effective quantities of 1 and 2, a pharmaceutically acceptable carrier. In another aspect the present invention relates to the abovementioned pharmaceutical compositions which do not contain any pharmaceutically acceptable carrier in addition to therapeutically effective quantities of 1 and 2.

The present invention also relates to the use of therapeutically effective quantities of the salts 1 for preparing a pharmaceutical composition also containing 2 for treating inflammatory or obstructive diseases of the respiratory tract. Preferably, the present invention relates to the abovementioned use for preparing a pharmaceutical composition for treating asthma or COPD.

Within the scope of the present invention the compounds 1 and 2 may be administered simultaneously or successively, while it is preferable according to the invention to administer compounds 1 und 2 simultaneously.

The present invention further relates to the use of therapeutically effect amounts of 1 and 2 for treating inflammatory or obstructive respiratory complaints, particularly asthma or COPD.

The proportions in which the active substances 1 and 2 may be used in the active substance combinations according to the invention are variable. Active substances 1 and 2 may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds 1 and 2, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various compounds and their different potencies. In general the combinations according to the invention may contain the components 1 and 2 generally in weight ratios in the range from 1:400 to 150:1, preferably in a weight ratio in the range from 1: 350 to 100:1.

The pharmaceutical compositions according to the invention containing the combinations of 1 and 2 are normally used so that 1 and 2 (values based on free base) are administered together in doses of 0.01 to 10000 µg, preferably 0.1 to 5000 µg, particularly preferably from 0.5 to 1000 µg per single dose.

In case the composition according to the invention contains a tiotropium salt as the anticholinergic component 1, the combination of active substances according to the invention may contain tiotropium cation 1' and the compound of formula 2 (based on free base) in the range from 1:300 to 50:1, preferably from 1:200 to 30:1, particularly preferably from 1:150 to 20:1, more preferably from 1:50 to 15:1. For example, without restricting the scope of the invention, preferred combinations of 1 and 2 according to the invention may contain tiotropium 1' and 2 (values based on free base) in the following weight ratios: 1:35, 1:34, 1:33, 1:32, 1:31, 1:30, 1:29, 1:29, 1:27, 1:26, 1:25, 1:24, 1:23, 1:22, 1:21, 1:20, 1:19, 1:18, 1:17, 1:16, 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1. The pharmaceutical compositions according to the invention containing the combinations of tiotropium as ingredient 1 and 2 are preferably administered so that 1' (tiotropium cation) and 2 (values based on free base) are present together in dosages of 5 to 500 μg, preferably, according to the invention, from 10 to 200 μg per single dose.

For example, combinations of 1 and 2 according to the invention contain an amount of tiotropium 1' and compound 2 (values based on free base) such that the total dosage per single dose is 10μg, 15μg, 20μg, 25μg, 30μg, 35μg, 45μg, 50μg, 55μg, 60μg, 65μg, 70μg, 75μg, 80μg, 85μg, 90μg, 95μg, 100μg, 105μg, 110μg, 115μg, 120μg, 125μg, 130μg, 135μg, 140μg, 145μg, 150μg, 155μg, 160μg, 165μg, 170μg, 175μg, 180μg, 185μg, 190μg, 195μg, 200μg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 μg, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances 1' and 2 may be present in the weight ratios given above.

For example, without restricting the scope of the invention, the combinations of 1 and 2 according to the invention may contain an amount of tiotropium 1' and compound 2 (values based on free base) such that 5μg of 1' and 5μg of 2, 5μg of 1' and 10μg of 2, 5μg of 1' and 15μg of 2, 5μg of 1' and 25μg of 2, 5μg of 1' and 50μg of 2, 5μg of 1' and 100μg of 2, 10μg of 1' and 5μg of 2, 10μg of 1' and 10μg of 2, 10μg of 1' and 15μg of 2, 10μg of 1' and 25μg of 2, 10μg of 1' and 50μg of 2, 10μg of 1' and 100μg of 2, 18μg of 1' and 5μg of 2, 18μg of 1' and 10μg of 2, 18μg of 1' and 15μg of 2, 18μg of 1' and 25μg of 2, 18μg of 1' and 50μg of 2, 18μg of 1' and 100μg of 2, 36μg of 1' and 5μg of 2, 36μg of 1' and 10μg of 2, 36μg of 1' and 15μg of 2, 36μg of 1' and 25μg of 2, 36μg of 1' and 50μg

of 2, 36μg of 1' and 100μg of 2, 40μg of 1' and 5μg of 2, 40μg of 1' and 10μg of 2, 40μg of 1' and 15μg of 2, 40μg of 1' and 25μg of 2, 40μg of 1' and 50μg of 2 or 40μg of 1' and 100μg of 2 are administered per single dose.

From the aforementioned examples for suitable doses of the tiotropium containing combinations according to the invention, the corresponding amounts of the salts 1 and of the acid addition salts of 2 are readily calculable.

In case the composition according to the invention contains a salt of formula 1a as the anticholinergic component 1, the combination of active substances according to the invention may contain cation 1a' and the compound of formula 2 (based on free base) for example in the following ratios by weight: 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1.

The pharmaceutical compositions according to the invention containing the combinations of 1a and 2 are preferably administered so that 1a' and 2 (values based on free base) are present together in dosages of 10 to 2000μg, preferably from 15 to 1000μg, even more preferably from 20 to 900μg per single dose.

For example, combinations of 1a and 2 according to the invention contain an amount of the 1a' and 2 (based on free base) such that the total dosage per single dose is about 15μg, 20μg, 25μg, 30μg, 35μg, 45μg, 50μg, 55μg, 60μg, 65μg, 70μg, 75μg, 80μg, 85μg, 90μg, 95μg, 100μg, 105μg, 110μg, 115μg, 120μg, 125μg, 130μg, 135μg, 140μg, 145μg, 150μg, 155μg, 160μg, 165μg, 170μg, 175μg, 180μg, 185μg, 190μg, 195μg, 200μg, 205μg, 210μg, 215μg, 220μg, 225μg, 230μg, 235μg, 240μg, 245μg, 250μg, 255μg, 260μg, 265μg, 270μg, 275μg, 280μg, 285μg, 290μg, 295μg, 300μg, 305μg, 310μg, 315μg, 320μg, 325μg, 330μg, 335μg, 340μg, 345μg, 350μg, 355μg, 360μg, 365μg, 370μg, 375μg, 380μg, 385μg, 390μg, 395μg, 400μg, 405μg, 410μg, 415μg, 420μg, 425μg, 430μg, 435μg, 440μg, 445μg, 450μg, 455μg, 460μg, 465μg, 470μg, 475μg, 480μg, 485μg, 490μg, 495μg, 500μg, 505μg, 510μg, 515μg, 520μg, 525μg, 530μg, 535μg, 540μg, 545μg, 550μg, 555μg, 560μg, 565μg, 570μg, 575μg, 580μg, 585μg, 590μg, 595μg, 600μg, 605μg, 610μg, 615μg, 620μg, 625μg, 630μg, 635μg, 640μg, 645μg, 650μg, 655μg, 660μg, 665μg, 670μg, 675μg, 680μg, 685μg, 690μg, 695μg, 700μg,

605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg, 705µg, 710µg, 715µg, 720µg, 725µg, 730µg, 735µg, 740µg, 745µg, 750µg, 755µg, 760µg, 765µg, 770µg, 775µg, 780µg, 785µg, 790µg, 795µg, 800µg, 805µg, 810µg, 815µg, 820µg, 825µg, 830µg, 835µg, 840µg, 845µg, 850µg, 855µg, 860µg, 865µg, 870µg, 875µg, 880µg, 885µg, 890µg, 895µg, 900µg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 µg, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances **1a'** and **2** may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the pharmaceutical compositions according to the invention may contain for instance the following quantities for each single dose: 20µg of **1a'** and 5µg of **2**, 20µg of **1a'** and 10µg of **2**, 20µg of **1a'** and 15µg of **2**, 20µg of **1a'** and 25µg of **2**, 20µg of **1a'** and 50µg of **2**, 20µg of **1a'** and 100µg of **2**, 40µg of **1a'** and 5µg of **2**, 40µg of **1a'** and 10µg of **2**, 40µg of **1a'** and 15µg of **2**, 40µg of **1a'** and 25µg of **2**, 40µg of **1a'** and 50µg of **2**, 40µg of **1a'** and 100µg of **2**, 60µg of **1a'** and 5µg of **2**, 60µg of **1a'** and 10µg of **2**, 60µg of **1a'** and 15µg of **2**, 60µg of **1a'** and 25µg of **2**, 60µg of **1a'** and 50µg of **2**, 60µg of **1a'** and 100µg of **2**, 100µg of **1a'** and 5µg of **2**, 100µg of **1a'** and 10µg of **2**, 100µg of **1a'** and 15µg of **2**, 100µg of **1a'** and 25µg of **2**, 100µg of **1a'** and 50µg of **2**, 100µg of **1a'** and 100µg of **2**, 200µg of **1a'** and 5µg of **2**, 200µg of **1a'** and 10µg of **2**, 200µg of **1a'** and 15µg of **2**, 200µg of **1a'** and 25µg of **2**, 200µg of **1a'** and 50µg of **2**, 200µg of **1a'** and 100µg of **2**, 300µg of **1a'** and 5µg of **2**, 300µg of **1a'** and 10µg of **2**, 300µg of **1a'** and 15µg of **2**, 300µg of **1a'** and 25µg of **2**, 300µg of **1a'** and 50µg of **2**, 300µg of **1a'** and 100µg of **2**, 400µg of **1a'** and 5µg of **2**, 400µg of **1a'** and 10µg of **2**, 400µg of **1a'** and 15µg of **2**, 400µg of **1a'** and 25µg of **2**, 400µg of **1a'** and 50µg of **2**, 400µg of **1a'** and 100µg of **2**, 500µg of **1a'** and 5µg of **2**, 500µg of **1a'** and 10µg of **2**, 500µg of **1a'** and 15µg of **2**, 500µg of **1a'** and 25µg of **2**, 500µg of **1a'** and 50µg of **2**, 500µg of **1a'** and 100µg of **2**, 600µg of **1a'** and 5µg of **2**, 600µg of **1a'** and 10µg of **2**, 600µg of **1a'** and 15µg of **2**, 600µg of **1a'** and 25µg of **2**, 600µg of **1a'** and 50µg of **2**, 600µg of **1a'** and 100µg of **2**, 700µg of **1a'** and 5µg of **2**, 700µg of **1a'** and 10µg of **2**, 700µg of **1a'** and 15µg of **2**, 700µg of **1a'** and 25µg of **2**, 700µg of **1a'** and 50µg of **2**, 700µg of **1a'** and 100µg of **2**, 800µg of **1a'** and 5µg of **2**, 800µg of **1a'** and 10µg of **2**, 800µg of **1a'** and 15µg of **2**, 800µg of **1a'** and 25µg of **2**,

800μg of **1a'** and 50μg of **2**, 800μg of **1a'** and 100μg of **2**, 900μg of **1a'** and 5μg of **2**, 900μg of **1a'** and 10μg of **2**, 900μg of **1a'** and 15μg of **2**, 900μg of **1a'** and 25μg of **2**, 900μg of **1a'** and 50μg of **2**, 900μg of **1a'** and 100μg of **2**, 1000μg of **1a'** and 5μg of **2**, 1000μg of **1a'** and 10μg of **2**, 1000μg of **1a'** and 15μg of **2**, 1000μg of **1a'** and 25μg of **2**, 1000μg of **1a'** and 50μg of **2**, 1000μg of **1a'** and 100μg of **2**.

From the aforementioned examples for suitable doses of the **1a'** containing combinations according to the invention, the corresponding amounts of the salts **1a** and of the acid addition salts of **2** are readily calculable.

In case the composition according to the invention contains a salt of formula **1c** as the anticholinergic component **1**, the combination of active substances according to the invention may contain cation **1c'** and the compound of formula **2** (based on free base) for example in the following ratios by weight: 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1.

The pharmaceutical compositions according to the invention containing the combinations of **1c** and **2** are preferably administered so that the cation **1c'** and **2** (values based on free base) are present together in dosages of 10 to 2000μg, more preferably from 15 to 1000μg, even more preferably from 20 to 800μg, and preferably according to the invention from 30 to 750μg, preferably from 40 to 700μg per single dose.

For example, combinations of **1c** and **2** according to the invention contain an amount of **1c'** and **2** (values based on free base) such that the total dosage per single dose is about 15μg, 20μg, 25μg, 30μg, 35μg, 45μg, 50μg, 55μg, 60μg, 65μg, 70μg, 75μg, 80μg, 85μg, 90μg, 95μg, 100μg, 105μg, 110μg, 115μg, 120μg, 125μg, 130μg, 135μg, 140μg, 145μg, 150μg, 155μg, 160μg, 165μg, 170μg, 175μg, 180μg, 185μg, 190μg, 195μg, 200μg, 205μg, 210μg, 215μg, 220μg, 225μg, 230μg, 235μg, 240μg, 245μg, 250μg, 255μg, 260μg, 265μg, 270μg, 275μg, 280μg, 285μg, 290μg, 295μg, 300μg, 305μg, 310μg, 315μg, 320μg, 325μg, 330μg, 335μg, 340μg, 345μg, 350μg, 355μg, 360μg, 365μg, 370μg, 375μg, 380μg, 385μg, 390μg, 395μg, 400μg, 405μg, 410μg, 415μg, 420μg, 425μg, 430μg, 435μg, 440μg, 445μg, 450μg, 455μg, 460μg, 465μg, 470μg, 475μg, 480μg, 485μg, 490μg, 495μg, 500μg, 505μg, 510μg, 515μg, 520μg, 525μg, 530μg, 535μg,

540μg, 545μg, 550μg, 555μg, 560μg, 565μg, 570μg, 575μg, 580μg, 585μg, 590μg, 595μg, 600μg, 605μg, 610μg, 615μg, 620μg, 625μg, 630μg, 635μg, 640μg, 645μg, 650μg, 655μg, 660μg, 665μg, 670μg, 675μg, 680μg, 685μg, 690μg, 695μg, 700μg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 μg, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances **1c'** and **2** may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations of **1c** and **2** according to the invention may contain a quantity of cation **1c'** and **2** (values based on free base) such that, for each single dose, 8.3μg of **1c'** and 5μg of **2**, 8.3μg of **1c'** and 10μg of **2**, 8.3μg of **1c'** and 15μg of **2**, 8.3μg of **1c'** and 25μg of **2**, 8.3μg of **1c'** and 50μg of **2**, 8.3μg of **1c'** and 100μg of **2**, 16.5μg of **1c'** and 5μg of **2**, 16.5μg of **1c'** and 10μg of **2**, 16.5μg of **1c'** and 15μg of **2**, 16.5μg of **1c'** and 25μg of **2**, 16.5μg of **1c'** and 50μg of **2**, 16.5μg of **1c'** and 100μg of **2**, 33.0μg of **1c'** and 5μg of **2**, 33.0μg of **1c'** and 10μg of **2**, 33.0μg of **1c'** and 15μg of **2**, 33.0μg of **1c'** and 25μg of **2**, 33.0μg of **1c'** and 50μg of **2**, 33.0μg of **1c'** and 100μg of **2**, 49.5μg of **1c'** and 5μg of **2**, 49.5μg of **1c'** and 10μg of **2**, 49.5μg of **1c'** and 15μg of **2**, 49.5μg of **1c'** and 25μg of **2**, 49.5μg of **1c'** and 50μg of **2**, 49.5μg of **1c'** and 100μg of **2**, 82.6μg of **1c'** and 5μg of **2**, 82.6μg of **1c'** and 10μg of **2**, 82.6μg of **1c'** and 15μg of **2**, 82.6μg of **1c'** and 25μg of **2**, 82.6μg of **1c'** and 50μg of **2**, 82.6μg of **1c'** and 100μg of **2**, 165.1μg of **1c'** and 5μg of **2**, 165.1μg of **1c'** and 10μg of **2**, 165.1μg of **1c'** and 15μg of **2**, 165.1μg of **1c'** and 25μg of **2**, 165.1μg of **1c'** and 50μg of **2**, 165.1μg of **1c'** and 100μg of **2**, 206.4μg of **1c'** and 5μg of **2**, 206.4μg of **1c'** and 10μg of **2**, 206.4μg of **1c'** and 15μg of **2**, 206.4μg of **1c'** and 25μg of **2**, 206.4μg of **1c'** and 50μg of **2**, 206.4μg of **1c'** and 100μg of **2**, 412.8μg of **1c'** and 5μg of **2**, 412.8μg of **1c'** and 10μg of **2**, 412.8μg of **1c'** and 15μg of **2**, 412.8μg of **1c'** and 25μg of **2**, 412.8μg of **1c'** and 50μg of **2**, 412.8μg of **1c'** and 100μg of **2** are present, for example.

From the aforementioned examples for suitable doses of the **1c'** containing combinations according to the invention, the corresponding amounts of the salts **1c** and of the acid addition salts of **2** are readily calculable.

For compositions according to the invention that contain as the anticholinergic a compound of formula **1d** the weigth ratios and amounts of **1d** and **2** are in the range of those suggested hereinbefore for combinations containing **1c** and **2**.

In case the composition according to the invention contains a salt of formula **1e** as the anticholinergic component **1**, the combination of active substances according to the invention may contain cation **1e'** and the compound of formula **2** (based on free base) for example in the following ratios by weight: 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1.

The pharmaceutical compositions according to the invention containing the combinations of **1e** and **2** are preferably administered so that the cation **1e'** and **2** (values based on free base) are present together in dosages of 5 to 2000μg, more preferably from 15 to 1000μg, even more preferably from 20 to 800μg, and preferably according to the invention from 30 to 750μg, preferably from 40 to 700μg per single dose.

For example, combinations of **1e** and **2** according to the invention contain an amount of **1e'** and **2** (values based on free base) such that the total dosage per single dose is about 15μg, 20μg, 25μg, 30μg, 35μg, 45μg, 50μg, 55μg, 60μg, 65μg, 70μg, 75μg, 80μg, 85μg, 90μg, 95μg, 100μg, 105μg, 110μg, 115μg, 120μg, 125μg, 130μg, 135μg, 140μg, 145μg, 150μg, 155μg, 160μg, 165μg, 170μg, 175μg, 180μg, 185μg, 190μg, 195μg, 200μg, 205μg, 210μg, 215μg, 220μg, 225μg, 230μg, 235μg, 240μg, 245μg, 250μg, 255μg, 260μg, 265μg, 270μg, 275μg, 280μg, 285μg, 290μg, 295μg, 300μg, 305μg, 310μg, 315μg, 320μg, 325μg, 330μg, 335μg, 340μg, 345μg, 350μg, 355μg, 360μg, 365μg, 370μg, 375μg, 380μg, 385μg, 390μg, 395μg, 400μg, 405μg, 410μg, 415μg, 420μg, 425μg, 430μg, 435μg, 440μg, 445μg, 450μg, 455μg, 460μg, 465μg, 470μg, 475μg, 480μg, 485μg, 490μg, 495μg, 500μg, 505μg, 510μg, 515μg, 520μg, 525μg, 530μg, 535μg, 540μg, 545μg, 550μg, 555μg, 560μg, 565μg, 570μg, 575μg, 580μg, 585μg, 590μg, 595μg, 600μg, 605μg, 610μg, 615μg, 620μg, 625μg, 630μg, 635μg, 640μg, 645μg, 650μg, 655μg, 660μg, 665μg, 670μg, 675μg, 680μg, 685μg, 690μg, 695μg, 700μg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 μg, particularly in the decimal range, are also included,

as will be apparent to the skilled man. In these dosage ranges, the active substances **1e'** and **2** may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations of **1e** and **2** according to the invention may contain a quantity of cation **1e'** and **2** (values based on free base) such that, for each single dose, 8.2μg of **1e'** and 5μg of **2**, 8.2μg of **1e'** and 10μg of **2**, 8.2μg of **1e'** and 15μg of **2**, 8.2μg of **1e'** and 25μg of **2**, 8.2μg of **1e'** and 50μg of **2**, 8.2μg of **1e'** and 100μg of **2**, 16.5μg of **1e'** and 5μg of **2**, 16.5μg of **1e'** and 10μg of **2**, 16.5μg of **1e'** and 15μg of **2**, 16.5μg of **1e'** and 25μg of **2**, 16.5μg of **1e'** and 50μg of **2**, 16.5μg of **1e'** and 100μg of **2**, 33.0μg of **1e'** and 5μg of **2**, 33.0μg of **1e'** and 10μg of **2**, 33.0μg of **1e'** and 15μg of **2**, 33.0μg of **1e'** and 25μg of **2**, 33.0μg of **1e'** and 50μg of **2**, 33.0μg of **1e'** and 100μg of **2**, 49.5μg of **1e'** and 5μg of **2**, 49.5μg of **1e'** and 10μg of **2**, 49.5μg of **1e'** and 15μg of **2**, 49.5μg of **1e'** and 25μg of **2**, 49.5μg of **1e'** and 50μg of **2**, 49.5μg of **1e'** and 100μg of **2**, 82.5μg of **1e'** and 5μg of **2**, 82.5μg of **1e'** and 10μg of **2**, 82.5μg of **1e'** and 15μg of **2**, 82.5μg of **1e'** and 25μg of **2**, 82.5μg of **1e'** and 50μg of **2**, 82.5μg of **1e'** and 100μg of **2**, 165.0μg of **1e'** and 5μg of **2**, 165.0μg of **1e'** and 10μg of **2**, 165.0μg of **1e'** and 15μg of **2**, 165.0μg of **1e'** and 25μg of **2**, 165.0μg of **1e'** and 50μg of **2**, 165.0μg of **1e'** and 100μg of **2**, 206.2μg of **1e'** and 5μg of **2**, 206.2μg of **1e'** and 10μg of **2**, 206.2μg of **1e'** and 15μg of **2**, 206.2μg of **1e'** and 25μg of **2**, 206.2μg of **1e'** and 50μg of **2**, 206.2μg of **1e'** and 100μg of **2**, 412.5μg of **1e'** and 5μg of **2**, 412.5μg of **1e'** and 10μg of **2**, 412.5μg of **1e'** and 15μg of **2**, 412.5μg of **1e'** and 25μg of **2**, 412.5μg of **1e'** and 50μg of **2**, 412.5μg of **1e'** and 100μg of **2** are present, for example.

From the aforementioned examples for suitable doses of the **1e'** containing combinations according to the invention, the corresponding amounts of the salts **1e** and of the acid addition salts of **2** are readily calculable.

For compositions according to the invention that contain as the anticholinergic a compound of formula **1f** or **1g** the weigth ratios and amounts of **1f**/**1g** and **2** are in the range of those suggested hereinbefore for combinations containing **1e** and **2**.

The aforementioned examples of possible doses applicable for the combinations according to the invention are to be understood as referring to doses per single application. However, these examples are not be understood as excluding the possibility of administering the combinations according to the invention multiple times. Depending on the medical need

patients may receive also multiple inhalative applications. As an example patients may receive the combinations according to the invention for instance two or three times (e.g. two or three puffs with a powder inhaler, an MDI etc) in the morning of each treatment day. As the aforementioned dose examples are only to be understood as dose examples per single application (i.e. per puff) multiple application of the combinations according to the invention leads to multiple doses of the aforementioned examples. The application of the combositions according to the invention can be for instance once a day, or depending on the duration of action of the anticholinergic agent twice a day, or once every 2 or 3 days.

Moreover it is emphazised that the aforementioned dose examples are to be understood as examples of metered doses only. In other terms, the aforementioned dose examples are not to be understood as the effective doses of the combinations according to the invention that do in fact reach the lung. It is clear for the person of ordinary skill in the art that the delivered dose to the lung is generally lower than the metered dose of the administered active ingredients.

The active substance combinations of 1 and 2 according to the invention are preferably administered by inhalation. For this purpose, ingredients 1 and 2 have to be made available in forms suitable for inhalation. Inhalable preparations according to the invention include inhalable powders, propellant-containing metered dose aerosols or propellant-free inhalable solutions. Inhalable powders according to the invention containing the combination of active substances 1 and 2 may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention, the term carrier may optionally be used instead of the term excipient. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The preparations according to the invention may contain the combination of active substances 1 and 2 either together in one formulation or in two separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

A) Inhalable powder containing the combinations of active substances 1 and 2 according to the invention:

The inhalable powders according to the invention may contain 1 and 2 either on their own or in admixture with suitable physiologically acceptable excipients.

If the active substances 1 and 2 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), cyclodextrines (e.g. α-cyclodextrine, β-cyclodextrine, χ-cyclodextrine, methyl-β-cyclodextrine, hydroxypropyl-β-cyclodextrine), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose, trehalose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates.

Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to 250μm, preferably between 10 and 150μm, most preferably between 15 and 80μm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9μm to the excipient mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance 1 and 2, preferably with an average particle size of 0.5 to 10μm, more preferably from 1 to 6μm, is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and by finally mixing the ingredients together are known from the prior art. The inhalable powders according to the invention may be prepared and administered either in the form of a single powder mixture which contains both 1 and 2 or in the form of separate inhalable powders which contain only 1 or 2.

The inhalable powders according to the invention may be administered using inhalers known from the prior art. Inhalable powders according to the invention which contain one or more physiologically acceptable excipients in addition to 1 and 2 may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630, or by other means as described in DE 36 25 685. The inhalable powders according to the invention which contain 1 and 2 optionally in conjunction with a physiologically acceptable excipient may be administered, for example, using the inhaler known by the name Turbuhaler® or using inhalers as disclosed for example in EP 237507. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to 1 and 2 are

packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

A particularly preferred inhaler for using the pharmaceutical combination according to the invention in capsules is shown in Figure 1.
This inhaler for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured via a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, and a mouthpiece 12 which is connected to the housing 1, the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut, as well as airholes 13 for adjusting the flow resistance.

If the inhalable powders according to the invention are packed into capsules (inhalers) for the preferred use described above, the quantities packed into each capsule should be 1 to 30mg per capsule. These capsules contain, according to the invention, either together or separately, the doses of 1 and 2 mentioned hereinbefore for each single dose.

B) Propellant gas-driven inhalation aerosols containing the combinations of active substances 1 and 2:
Inhalation aerosols containing propellant gas according to the invention may contain substances 1 and 2 dissolved in the propellant gas or in dispersed form. 1 and 2 may be present in separate formulations or in a single preparation, in which 1 and 2 are either both dissolved, both dispersed or only one component is dissolved and the other is dispersed.
The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof.
Particularly preferred propellant gases are halogenated alkane derivatives selected from TG11, TG12, TG134a (1,1,1,2-tetrafluoroethane) and TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof, of which the propellant gases TG134a, TG227 and mixtures thereof are preferred.

The propellant-driven inhalation aerosols according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

The inhalation aerosols containing propellant gas according to the invention may contain up to 5 wt.-% of active substance 1 and/or 2. Aerosols according to the invention contain, for example, 0.002 to 5 wt.-%, 0.01 to 3 wt.-%, 0.015 to 2 wt.-%, 0.1 to 2 wt.-%, 0.5 to 2 wt.-% or 0.5 to 1 wt.-% of active substance 1 and/or 2.

If the active substances 1 and/or 2 are present in dispersed form, the particles of active substance preferably have an average particle size of up to 10μm, preferably from 0.1 to 6μm, more preferably from 1 to 5μm.

The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers). Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of propellant-driven aerosols as hereinbefore described combined with one or more inhalers suitable for administering these aerosols. In addition, the present invention relates to inhalers which are characterised in that they contain the propellant gas-containing aerosols described above according to the invention. The present invention also relates to cartridges fitted with a suitable valve which can be used in a suitable inhaler and which contain one of the above-mentioned propellant gas-containing inhalation aerosols according to the invention. Suitable cartridges and methods of filling these cartridges with the inhalable aerosols containing propellant gas according to the invention are known from the prior art.

C) Propellant-free inhalable solutions or suspensions containing the combinations of active substances 1 and 2 according to the invention:

Propellant-free inhalable solutions and suspensions according to the invention contain, for example, aqueous or alcoholic, preferably ethanolic solvents, optionally ethanolic solvents mixed with aqueous solvents. If aqueous/ethanolic solvent mixtures are used the relative proportion of ethanol compared with water is not limited but preferably the maximum is up to 70 percent by volume, more particularly up to 60 percent by volume of ethanol. The remainder of the volume is made up of water. The solutions or suspensions containing 1 and 2, separately or together, are adjusted to a pH of 2 to 7, preferably 2 to 5, using

suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

According to the invention, the addition of editic acid (EDTA) or one of the known salts thereof, sodium editate, as stabiliser or complexing agent is unnecessary in the present formulation. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium editate is less than 100mg/100ml, preferably less than 50mg/100 ml, more preferably less than 20mg/100 ml. Generally, inhalable solutions in which the content of sodium editate is from 0 to 10mg/100ml are preferred.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or

preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents. The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins and provitamins occurring in the human body.

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50mg/100ml, more preferably between 5 and 20mg/100ml.

Preferred formulations contain, in addition to the solvent water and the combination of active substances **1** and **2**, only benzalkonium chloride and sodium editate. In another preferred embodiment, no sodium editate is present.

The propellant-free inhalable solutions according to the invention are administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Within the scope of the present invention, preferred inhalers are those in which a quantity of less than 100µL, preferably less than 50µL, more preferably between 20 and 30µL of active substance solution can be nebulised in preferably one spray action to form an aerosol with an average particle size of less than 20µm, preferably less than 10µm, in such a way that the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

An apparatus of this kind for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687 (cf. in particular Figures 6a and 6b). The nebulisers (devices) described therein are known by the name Respimat®.
This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols according to the invention containing the combination of active substances **1** and **2**.
Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm

wide, this device can be carried at all times by the patient. The nebuliser sprays a defined volume of pharmaceutical formulation using high pressures through small nozzles so as to produce inhalable aerosols.

The preferred atomiser essentially consists of an upper housing part, a pump housing, a nozzle, a locking mechanism, a spring housing, a spring and a storage container, characterised by

- a pump housing which is secured in the upper housing part and which comprises at one end a nozzle body with the nozzle or nozzle arrangement,
- a hollow plunger with valve body,
- a power takeoff flange in which the hollow plunger is secured and which is located in the upper housing part,
- a locking mechanism situated in the upper housing part,
- a spring housing with the spring contained therein, which is rotatably mounted on the upper housing part by means of a rotary bearing,
- a lower housing part which is fitted onto the spring housing in the axial direction.

The hollow plunger with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is axially movable within the cylinder. Reference is made in particular to Figures 1 to 4, especially Figure 3, and the relevant parts of the description. The hollow plunger with valve body exerts a pressure of 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the fluid, the measured amount of active substance solution, at its high pressure end at the moment when the spring is actuated. Volumes of 10 to 50 microlitres are preferred, while volumes of 10 to 20 microlitres are particularly preferred and a volume of 15 microlitres per spray is most particularly preferred.

The valve body is preferably mounted at the end of the hollow plunger facing the valve body.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by microtechnology. Microstructured nozzle bodies are disclosed for example in WO 94/07607; reference is hereby made to the contents of this specification, particularly Figure 1 therein and the associated description.

The nozzle body consists for example of two sheets of glass and/or silicon firmly joined together, at least one of which has one or more microstructured channels which connect the nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth preferably being 4.5 to 6.5 microns while the length is preferably 7 to 9 microns.
In the case of a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may extend parallel to one another or may be inclined relative to one another in the direction of the nozzle opening. In a nozzle body with at least two nozzle openings at the outlet end the directions of spraying may be at an angle of 20 to 160° to one another, preferably 60 to 150°, most preferably 80 to 100°. The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, most preferably 30 to 70 microns. Spacings of 50 microns are most preferred. The directions of spraying will therefore meet in the vicinity of the nozzle openings.
The liquid pharmaceutical preparation strikes the nozzle body with an entry pressure of up to 600 bar, preferably 200 to 300 bar, and is atomised into an inhalable aerosol through the nozzle openings. The preferred particle or droplet sizes of the aerosol are up to 20 microns, preferably 3 to 10 microns.

The locking mechanism contains a spring, preferably a cylindrical helical compression spring, as a store for the mechanical energy. The spring acts on the power takeoff flange as an actuating member the movement of which is determined by the position of a locking member. The travel of the power takeoff flange is precisely limited by an upper and lower stop. The spring is preferably biased, via a power step-up gear, e.g. a helical thrust gear, by an external torque which is produced when the upper housing part is rotated counter to the spring housing in the lower housing part. In this case, the upper housing part and the power takeoff flange have a single or multiple V-shaped gear.

The locking member with engaging locking surfaces is arranged in a ring around the power takeoff flange. It consists, for example, of a ring of plastic or metal which is inherently radially elastically deformable. The ring is arranged in a plane at right angles to the atomiser axis. After the biasing of the spring, the locking surfaces of the locking member move into the path of the power takeoff flange and prevent the spring from relaxing. The locking member is actuated by means of a button. The actuating button is connected or coupled to the locking member. In order to actuate the locking mechanism, the actuating

button is moved parallel to the annular plane, preferably into the atomiser; this causes the deformable ring to deform in the annular plane. Details of the construction of the locking mechanism are given in WO 97/20590.

The lower housing part is pushed axially over the spring housing and covers the mounting, the drive of the spindle and the storage container for the fluid.
When the atomiser is actuated the upper housing part is rotated relative to the lower housing part, the lower housing part taking the spring housing with it. The spring is thereby compressed and biased by means of the helical thrust gear and the locking mechanism engages automatically. The angle of rotation is preferably a whole-number fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is biased, the power takeoff part in the upper housing part is moved along by a given distance, the hollow plunger is withdrawn inside the cylinder in the pump housing, as a result of which some of the fluid is sucked out of the storage container and into the high pressure chamber in front of the nozzle.

If desired, a number of exchangeable storage containers which contain the fluid to be atomised may be pushed into the atomiser one after another and used in succession. The storage container contains the aqueous aerosol preparation according to the invention.
The atomising process is initiated by pressing gently on the actuating button. As a result, the locking mechanism opens up the path for the power takeoff member. The biased spring pushes the plunger into the cylinder of the pump housing. The fluid leaves the nozzle of the atomiser in atomised form.

Further details of construction are disclosed in PCT Applications WO 97/12683 and WO 97/20590, to which reference is hereby made.
The components of the atomiser (nebuliser) are made of a material which is suitable for its purpose. The housing of the atomiser and, if its operation permits, other parts as well, are preferably made of plastics, e.g. by injection moulding. For medicinal purposes, physiologically safe materials are used.

Figures 6a/b of WO 97/12687, show the nebuliser (Respimat®) which can advantageously be used for inhaling the aqueous aerosol preparations according to the invention.

Figure 6a of WO 97/12687 shows a longitudinal section through the atomiser with the spring biased while Figure 6b of WO 97/12687 shows a longitudinal section through the atomiser with the spring relaxed.

The upper housing part (51) contains the pump housing (52) on the end of which is mounted the holder (53) for the atomiser nozzle. In the holder is the nozzle body (54) and a filter (55). The hollow plunger (57) fixed in the power takeoff flange (56) of the locking mechanism projects partially into the cylinder of the pump housing. At its end the hollow plunger carries the valve body (58). The hollow plunger is sealed off by means of the seal (59). Inside the upper housing part is the stop (60) on which the power takeoff flange abuts when the spring is relaxed. On the power takeoff flange is the stop (61) on which the power takeoff flange abuts when the spring is biased. After the biasing of the spring the locking member (62) moves between the stop (61) and a support (63) in the upper housing part. The actuating button (64) is connected to the locking member. The upper housing part ends in the mouthpiece (65) and is sealed off by means of the protective cover (66) which can be placed thereon.

The spring housing (67) with compression spring (68) is rotatably mounted on the upper housing part by means of the snap-in lugs (69) and rotary bearing. The lower housing part (70) is pushed over the spring housing. Inside the spring housing is the exchangeable storage container (71) for the fluid (72) which is to be atomised. The storage container is sealed off by the stopper (73) through which the hollow plunger projects into the storage container and is immersed at its end in the fluid (supply of active substance solution). The spindle (74) for the mechanical counter is mounted in the covering of the spring housing. At the end of the spindle facing the upper housing part is the drive pinion (75). The slider (76) sits on the spindle.

The nebuliser described above is suitable for nebulising the aerosol preparations according to the invention to produce an aerosol suitable for inhalation.

If the formulation according to the invention is nebulised using the method described above (Respimat®) the quantity delivered should correspond to a defined quantity with a tolerance of not more than 25%, preferably 20% of this amount in at least 97%, preferably at least 98% of all operations of the inhaler (spray actuations). Preferably, between 5 and 30 mg of formulation, most preferably between 5 and 20 mg of formulation are delivered as a defined mass on each actuation.

However, the formulation according to the invention may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers or other stationary nebulisers.

Accordingly, in a further aspect, the invention relates to pharmaceutical formulations in the form of propellant-free inhalable solutions or suspensions as described above combined with a device suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, the invention relates to propellant-free inhalable solutions or suspensions characterised by the combination of active substances **1** and **2** according to the invention in conjunction with the device known by the name Respimat®. In addition, the present invention relates to the above-mentioned devices for inhalation, preferably the Respimat®, characterised in that they contain the propellant-free inhalable solutions or suspensions according to the invention as described hereinbefore.
According to the invention, inhalable solutions which contain the active substances **1** and **2** in a single preparation are preferred. The term "single preparation" also includes preparations which contain the two ingredients **1** and **2** in two-chamber cartridges, as disclosed for example in WO 00/23037. Reference is hereby made to this publication in its entirety.

The propellant-free inhalable solutions or suspensions according to the invention may take the form of concentrates or sterile inhalable solutions or suspensions ready for use, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®. Formulations ready for use may be produced from the concentrates, for example, by the addition of isotonic saline solutions. Sterile formulations ready for use may be administered using energy-operated free-standing or portable nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

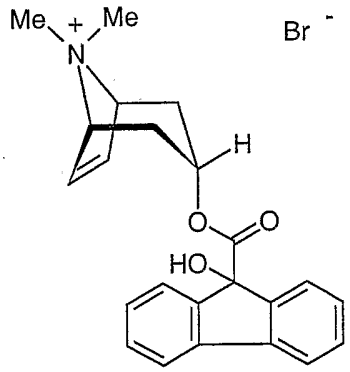
Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of propellant-free inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile formulations ready for use, combined with a device suitable for administering these solutions, characterised in that the device is an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other methods.

The Examples which follow serve to illustrate the present invention in more detail without restricting the scope of the invention to the following embodiments by way of example.

First, the preparation of exemplified compounds **1e**, **1f**, **1g** which are not known in the art will be described.

I) Examples and preparation of the compounds of formula 1e:

Example 1: tropenol 9-hydroxy-fluorene-9-carboxylate methobromide :



1.1.: methyl 9-hydroxy-fluorene-9-carboxylate:.

50.4 g (0.223 mol) of 9-hydroxy-9-fluorenecarboxylic acid are dissolved in 500 ml of methanol, combined with 5 ml (0.089 mol) of conc. sulphuric acid and refluxed for 1 hour. After cooling, 100 ml of sodium hydrogen carbonate solution (about pH 8) are added and the methanol is largely evaporated down. The mixture is extracted with dichloromethane and water, the organic phase is dried and evaporated to dryness. The product is purified by recrystallisation from ethyl acetate.

Yield: 50.0g of white crystals (= 93% of theory).

1.2: tropenol 9-hydroxy-fluorene-9-carboxylate:

13.4 g (0.056 mol) of methylester 1.1, 11.65 g (0.084 mol) of tropenol and 0.3 g of sodium are heated as a melt at 75 mbar for 4 h over a bath of boiling water with occasional agitation. After cooling the sodium residues are dissolved with acetonitrile, the solution is evaporated to dryness and the residue is extracted with dichloromethane/water. The organic phase is washed with water, dried over $MgSO_4$ and the solvent is distilled off. The product is purified by recrystallisation from diethyl ether.

Yield: 11.40 g of white crystals (= 29 % of theory).

1.3: tropenol 9-hydroxy-fluorene-9-carboxylate methobromide :

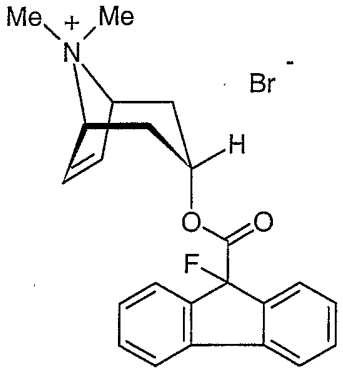
1.75 g (0.005 mol) of 1.2 are taken up in 30 ml dichloromethane and 15 ml acetonitrile and combined with 2.85 g (0.015 mol) of 50% methylbromide solution in acetonitrile. The reaction mixture is left to stand for 3 days at ambient temperature, during which time the product crystallises. The crystals precipitated are separated off and recrystallised from diethyl ether to purify them.

Yield: 1.95 g of white crystals (= 88 % of theory); Melting point: 250°C.

Elemental analysis: calculated: C (62.45) H (5.47) N (3.17)

found: C (61.53) H (5.84) N (3.22).

Example 2: tropenol 9-fluoro-fluorene-9-carboxylate methobromide :



2.1: tropenol 9-fluoro-fluorene-9-carboxylate:

1.66 ml (0.009 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are placed in 10 ml dichloromethane and within 20 minutes at 15°–20° C a solution of 2.4g (0.007 mol) of 1.2 in 25 ml dichloromethane is added dropwise thereto.

The mixture is stirred for 20 h at ambient temperature, cooled to 0°C and carefully combined with 80 ml of water with thorough stirring. Then the mixture is carefully adjusted to pH 8 with aqueous $NaHCO_3$ solution, the organic phase is separated off, the aqueous phase is extracted again with dichloromethane, the combined organic phases are washed with water, dried over $MgSO_4$ and evaporated to dryness. The hydrochloride is precipitated and recrystallised from acetonitrile/diethyl ether. Then the free base is liberated again using 10% aq. sodium carbonate solution. Yield: 1.05 g bright yellow crystals (= 53 % of theoretical)

2.2: tropenol 9-fluoro-fluorene-9-carboxylate methobromide :

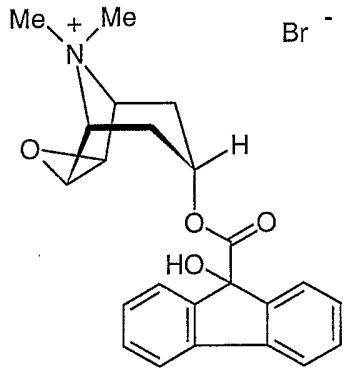
1.05 g (0.003 mol) of 2.1 are taken up in 20 ml acetonitrile and reacted with 1.71 g (0.009 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3. To purify it the product is recrystallised from acetonitrile.

Yield: 0.80 g of white crystals (= 60 % of theoretical); melting point: 252°C.

Elemental analysis: calculated: C (62.17) H (5.22) N (3.15)

found: C (62.04) H (5.23) N (3.15).

Example 3: scopine 9-hydroxy-fluorene-9-carboxylate methobromide :



3.1: scopine 9-hydroxy-fluorene-9-carboxylate:

9.0 g (0.026 mol) of tropenol ester 2.1 are suspended in 90 ml of dimethylformamide and combined with 0.47 g (0.003 mol) of vanadium-(V)-oxide. At 60°C a solution of 4.89 g (0.052 mol) of H_2O_2-urea in 20 ml of water is added dropwise and stirred for 6 hours at 60°C. After cooling to 20°C the precipitate formed is suction filtered, the filtrate is adjusted to pH 2 with 4 N hydrochloric acid and combined with $Na_2S_2O_5$ dissolved in water. The resulting solution is evaporated to dryness, the residue is extracted with dichloromethane/water. The acidic aqueous phase is made basic with Na_2CO_3, extracted with dichloromethane and the organic phase is dried over Na_2SO_4 and concentrated. Then 1 ml of acetylchloride is added at ambient temperature and the mixture is stirred for 1 hour. After extraction with 1 N hydrochloric acid the aqueous phase is made basic, extracted with dichloromethane, the organic phase is washed with water and dried over Na_2SO_4. Then the solvent is removed by distillation. The crude product is purified by recrystallisation from diethyl ether.

Yield: 2.8 g of white crystals (= 30 % of theoretical).

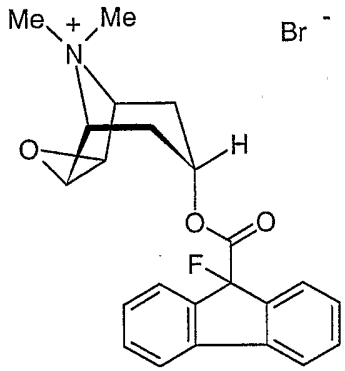
3.2: scopine 9-hydroxy-fluorene-9-carboxylate methobromide :

1.3 g (0.004 mol) 3.1 are taken up in 20 ml chloroform and 20 ml acetonitrile and reacted with 2.279 g (0.012 mol) of 50% methylbromide solution in acetonitrile analogously to step 1.3. To purify it the product is recrystallised from acetonitrile.

Yield: 1.25 g of light beige crystals (= 68 % of theoretical); melting point: 243-244°C.

Elemental analysis: calculated: C (60.27) H (5.28) N (3.06)
found: C (60.03) H (5.35) N (3.55).

Example 4: scopine 9-fluoro-fluorene-9-carboxylate methobromide :



4.1: scopine 9-fluoro-fluorene-9-carboxylate:

0.885 ml (0.005 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are placed in 25 ml of dichloromethane and reacted with 1.42 g (0.004 mol) of 3.1 analogously to the procedure according to 2.1.

Yield: 1.1 g beige crystals (= 75 % of theoretical)

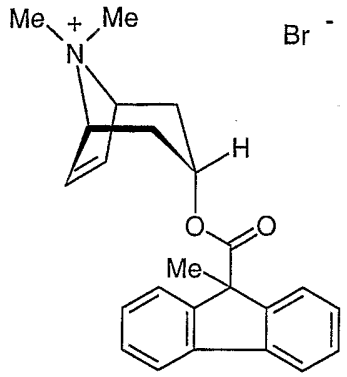
4.2: scopine 9-fluoro-fluorene-9-carboxylate methobromide :

1.1 g (0.003 mol) of 4.1 are taken up in 30 ml acetonitrile and reacted with 1.71 g (0.009 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3. To purify it the product is recrystallised from isopropanol.

Yield: 0.45 g of white crystals (= 33 % of theoretical); melting point: 200-201°C.

Elemental analysis: calculated: C (60.01) H (5.04) N (3.04)
found: C (59.91) H (5.18) N (3.10).

Example 5: tropenol 9-methyl-fluorene-9-carboxylate methobromide :



5.1.: 9-methyl-fluorene-9-carboxylic acid:.

a) methyl 9-methyl-fluorene-9-carboxylate:

From 7.6 g (0.33 mol) of sodium and 300 ml of ethanol a sodium ethoxide solution is prepared, to which 69.6 g (0.33 mol) of 9-fluorenecarboxylic acid are added batchwise. After the addition has ended the mixture is stirred for 2.5 hours at ambient temperature. Then it is evaporated to dryness, the residue is suspended in 600 ml of dimethylformamide and 93.96 g (0.662 mol) of methyl iodide are added dropwise. The mixture is stirred for 3 hours at constant temperature. The cloudy solution is stirred into 500 ml of water and 300 ml of diethyl ether with cooling and extracted, the organic phase is washed with water and 10% sodium carbonate solution, dried and evaporated to dryness. The residue is purified by column chromatography, eluant: cyclohexane / ethyl acetate 96:4.

Yield: 12.61 g of white crystals (= 16% of theoretical); melting point: 108°-109°C.

b) 9-methyl-fluorene-9-carboxylic acid:

12.6 g (0.053 mol) of methyl 9-methyl-fluorene-9-carboxylate and 53 ml of 2 molar, aqueous sodium hydroxide solution are stirred in 120 ml of 1,4-dioxane for 24 hours at ambient temperature. The dioxane is distilled off, made up to a total volume of 300 ml with water and extracted with diethyl ether. The aqueous phase is acidified with 3 molar, aqueous HCl, crystallised and filtered.

Yield: 11.25 g of white crystals (= 95% of theoretical); melting point: 168°-169°C.

5.2: tropenol 9-methyl-fluorene-9-carboxylate:

6.73 g (0.03 mol) of 5.1 are suspended in 60 ml dichloromethane, combined with 5.0 g of oxalyl chloride and 1 drop of dimethylformamide, then stirred for one hour at ambient temperature and finally the solvent is distilled off. The acid chloride remaining is used in the next step without any further purification.

4.18 g (0.03 mol) of tropenol and 4.27 g (0.033 mol) of diisopropylethylamine are suspended in 100 ml of dichloroethane, the acid chloride is added dropwise to 30 ml of dichloroethane at 35-40°C and then stirred for 24 hours at 40° C. The suspension is diluted with dichloromethane and extracted with dilute hydrochloric acid. The organic phase is then washed with water, dried over $MgSO_4$ and the product is converted into its hydrochloride with a solution of HCl in diethyl ether. The solvent is then removed. To purify it the precipitated hydrochloride is taken up in water and extracted with diethyl ether. The aqueous phase is made basic with 10% aq. sodium carbonate solution and extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and the solvent is distilled off.

Yield: 4.40 g of yellow oil (= 42% of theoretical);

5.3: tropenol 9-methyl-fluorene-9-carboxylate methobromide :

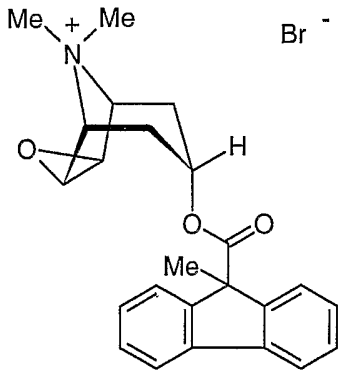
1.8 g (0.005 mol) of the free base 5.2 are reacted analogously to the method in step 1.3. The product is purified by recrystallisation from acetone.

Yield: 1.80 g of white crystals (= 82 % of theoretical); melting point: 258-259°C;

Elemental analysis: calculated: C (65.46) H (5.95) N (3.18)

found: C (64.15) H (5.95) N (3.18).

Example 6: scopine 9-methyl-fluorene-9-carboxylate methobromide :



6.1: scopine 9-methyl-fluorene-9-carboxylate:

2.5 g (0.007 mol) of tropenol ester 5.2 are reacted with 0.13 g (0.001 mol) of vanadium-(V)-oxide and 1.43 g (0.015 mol) of H_2O_2-urea analogously to the process according to step 3.1.

Yield: 1.8 g of white crystals (= 71 % of theoretical).

6.2: scopine 9-methyl-fluorene-9-carboxylate methobromide :

1.8 g (0.005 mol) of 6.1 are taken up in 30 ml acetonitrile and reacted with 2.848 g (0.015 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3.

Yield: 1.6 g of white crystals (= 70 % of theoretical); melting point: 214°C.

Elemental analysis: calculated: C (62.13) H (5.93) N (4.26)
found: C (62.23) H (6.05) N (4.32).

II) Examples and preparation of the compounds of formula 1f:

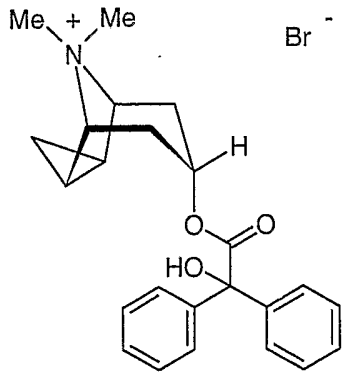
Preparation of starting material cyclopropyltropine:

35 ml (0.35 mol) of 40% aqueous potassium hydroxide solution is overlaid with 100 ml of diethyl ether and cooled in the ice bath. For this, 23.64 g (0.101 mol) of N-methyl-N-nitrosourea are added batchwise and then the mixture is stirred for about 10 minutes. The ether phase is decanted off and the solution obtained is used in the following step.

25 ml of the diazomethane solution prepared above are added to a solution of 4.01 g (0.028 mol) of tropenol in 25 ml of diethyl ether and 5 ml of methanol while cooling with an ice bath. Then 53.4 mg (0.000139 mol) of bis(benzonitrile)dichloro-palladium(II) are added. A further 28 ml of the diazomethane solution are then added batchwise. After about 1.5 hours the solvent is distilled off *in vacuo*, the residue remaining is extracted, this solution is filtered and the solvent is removed by distillation.

Yield: 4.25 g of slightly yellowish crystals (= 96% of theoretical)

Example 7: Cyclopropyltropine benzilate methobromide:



7.1.: methyl benzilate:

90 g (0.394 mol) of benzilic acid are dissolved in 900 ml acetonitrile and at 5°C 109.6 g (0.72 mol) of DBU are added dropwise. After the addition of 204.4 g (1.44 mol) of methyl iodide the mixture is stirred for 24 hours at ambient temperature (about 20-23°C). The solution is evaporated down to the residue, the residue is taken up in diethyl ether and extracted with water. The organic phase is washed with 5% aqueous sodium carbonate solution and water, dried and the solvent is distilled off. The product is purified by recrystallisation from cyclohexane. Yield: 77.19 g of white crystals (= 81% of theoretical) Melting point: 74°-76°C.

7.2.: cyclopropyltropine benzilate:

5.34 g (0.022 mol) methyl benzilate 7.1, 1.53 g (0.01 mol) of cyclopropyltropine and 0.25 g (0.01 mol) of sodium are heated as a melt over a bath of boiling water at 75 mbar for 1 h with occasional shaking. After cooling, the sodium residues are dissolved with acetonitrile, the solution is evaporated to dryness and the residue is extracted with dichloromethane/water. The organic phase is extracted with 10% potassium hydrogen sulphate solution, the resulting aqueous phase is made basic and extracted with dichloromethane. The organic phase is separated off, dried and evaporated to dryness. The product is purified by recrystallisation from acetonitrile. Yield: 2.41 g of white crystals (= 66 % of theoretical).

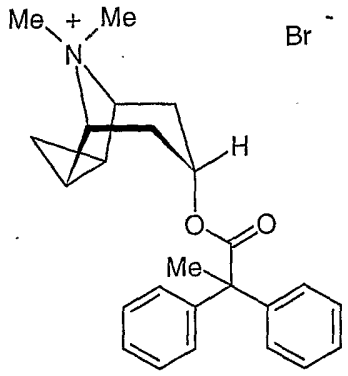
7.3: cyclopropyltropine benzilate methobromide :

0.46 g (0.0013 mol) of 7.2 are taken up in 5 ml acetonitrile and stirred with 1.53 g (0.0082 mol) of 50% methyl bromide solution in acetonitrile in a pressurised reaction vessel at 80°C. After 2 days the solution is evaporated to dryness, the residue is taken up in acetonitrile and filtered while hot. After cooling the precipitated crystals are separated off, dried and recrystallised from acetonitrile.

Yield: 0.066 g of white crystals (= 11 % of theoretical); melting point: 208-209°C.

Elemental analysis:	calculated:	C (62.89)	H (6.16)	N (3.06)
	found:	C (62.98)	H (6.20)	N (3.03).

Example 8: Cyclopropyltropine 2,2-diphenylpropionate methobromide:



8.1.: 2,2-Diphenylpropionic acid chloride:

52.08g (0.33 mol) oxalyl chloride are slowly added dropwise at 20°C to a suspension of 25.0 g (0.11 mol) of 2,2-diphenylpropionic acid, 100 ml of dichloromethane and 4 drops of dimethylformamide. It is stirred for 1 h at 20°C and 0.5 h at 50°C. The solvent is distilled off and the residue remaining is used in the next step without any further purification.

8.2: cyclopropyltropine 2,2-diphenylpropionate:

2.3 g (0.015 mol) of cyclopropyltropine and 2.13 g (0.016 mol) of diisopropylethylamine are placed in 30 ml of dichloromethane and within 15 minutes combined with a solution of acid chloride 8.1 in dichloromethane. Then the mixture is stirred for 2 hours at ambient temperature and 72 hours at 40°C. For working up it is washed with water, dried over $MgSO_4$ and the solvent is distilled off. The product is converted into its hydrochloride with a solution of HCl in diethyl ether. To purify it the precipitated hydrochloride is taken up in water and extracted with diethyl ether. The aqueous phase is made basic with 10% aq. sodium carbonate solution and extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and the solvent is distilled off.

Yield: 2.15 g of yellow oil (= 36% of theoretical)

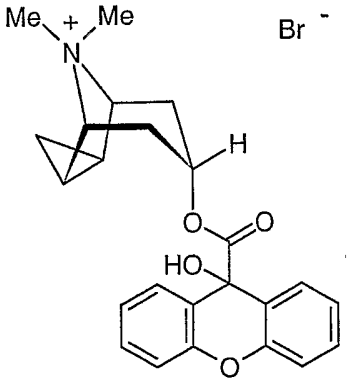
8.3: Cyclopropyltropine 2,2-diphenylpropionate methobromide :

1.8 g (0.005 mol) of the free base 8.2 are reacted analogously to the method in step 7.3. The purification is carried out by recrystallisation from acetonitrile/diethyl ether.

Yield: 1.53 g of white crystals (= 67 % of theoretical); melting point: 208-209°C;

Elemental analysis:	calculated:	C (65.79)	H (6,63)	N (3.07)
	found:	C (65.47)	H (6.77)	N (3.03).

Example 9: Cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide :



9.1.: methyl 9-hydroxy-xanthene-9-carboxylate:

a) methyl xanthene-9-carboxylate:

A sodium ethoxide solution is generated from 21.75 g (0.95 mol) of sodium and 1500 ml of ethanol. 214 g (0.95 mol) of xanthene-9-carboxylic acid is added batchwise to this solution and the resulting suspension is stirred for 1 hour at ambient temperature. Then the solid is separated off, washed with 1500 ml of diethyl ether, the isolated crystals are suspended in 1500 ml of dimethylformamide and 126.73 ml (2.0 mol) of methyl iodide are added with stirring. The solution obtained is left to stand for 24 hours at ambient temperature, then diluted with water to a total volume of 6 l, crystallised, suction filtered, washed with water and dried.

Yield: 167 g of white crystals 7 (= 74% of theoretical)

Melting point: 82°C.

b) methyl 9-hydroxy-xanthene-9-carboxylate:

48.05 g (0.2 mol) of methyl xanthene-9-carboxylate are dissolved in 1200 ml of tetrahydrofuran and combined with 23.63 g (0.2 mol) of potassium tert. butoxide at 0°C. Oxygen is then piped in for 2 hours at –10° to –5°C, then the mixture is acidified with 2 N aqueous hydrochloric acid and most of the solvent is removed by distillation. The residue remaining is extracted with ethyl acetate and water, the organic phase is extracted with aqueous Na2S2O5 solution, washed with water, dried and the solvent is distilled off.

The product is purified by crystallisation from diisopropylether and cyclohexane. Yield: 11.10 g of white crystals (= 22% of theoretical)

9.2: cyclopropyltropine [9-hydroxy-xanthene-9-carboxylate] :

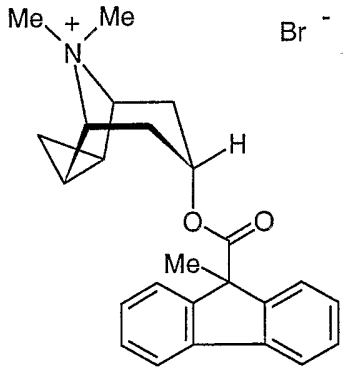
6.0 g (0.023 mol) 9.1, 3.065 g (0.02 mol) cyclopropyltropine and 0.02 g sodium are reacted analogously to step 7.2. Yield: 2.2 g of white crystals(= 25 % of theoretical);
Melting point: 115-116°C.

9.3: cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide :

2.1 g (0.006 mol) of the free base 9.2 are reacted analogously to the method in step 7.3. The purification is carried out by recrystallisation from isopropanol.
Yield: 1.05 g of beige crystals (= 37 % of theoretical); melting point: 218°C;

Elemental analysis:	calculated:	C (61.02)	H (5.55)	N (2.97)
	found:	C (60.40)	H (5.72)	N (2.96).

Example 10: cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide :



10.1.: 9-methyl-fluorene-9-carboxylic acid:

a) methyl 9-methyl-fluorene-9-carboxylate:
A sodium ethoxide solution is prepared from 7.6 g (0.33 mol) sodium and 300 ml of ethanol, and 69.6 g (0.33 mol) of 9-fluorenecarboxylic acid are added batchwise thereto. After the addition has ended it is stirred for 2.5 hours at ambient temperature. Then it is evaporated to dryness, the residue is suspended in 600 ml of dimethylformamide and 93.96 g (0.662 mol) of methyl iodide is added dropwise. The mixture is stirred for 3 hours at constant temperature. The cloudy solution is stirred into 500 ml of water and 300 ml diethyl ether with cooling, and extracted, the organic phase is washed with water and 10% sodium carbonate solution, dried and evaporated to dryness. The residue is purified by column chromatography, eluant: cyclohexane / ethyl acetate 96:4.
Yield: 12.61 g of white crystals (= 16% of theoretical); melting point: 108°-109°C.

b) 9-methyl-fluorene-9-carboxylic acid:

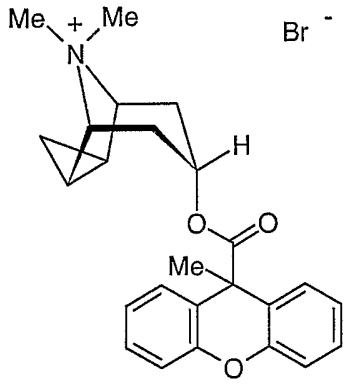
12.6 g (0.053 mol) of methyl 9-methyl-fluorene-9-carboxylate and 53 ml of 2 molar aqueous sodium hydroxide solution are stirred in 120 ml of 1,4-dioxane for 24 hours at ambient temperature. The dioxane is distilled off, water is added to give a total volume of 300 ml and the mixture is extracted with diethyl ether. The aqueous phase is acidified with 3 molar aqueous HCl, crystallised and filtered.
Yield: 11.25 g of white crystals (= 95% of theoretical); melting point: 168°-169°C.

10.2: cyclopropyltropine 9-methyl-fluorene-9-carboxylate:
The acid chloride is prepared from 4.0 g (0.018 mol) of 10.1, 4.53 g (0.036 mol) of oxalyl chloride and 4 drops of dimethylformamide in 40 ml dichloromethane. 2.48 g (0.016 mol) of cyclopropyltropine and 1.91 g (0.019 mol) of triethylamine are suspended in 30 ml of dichloroethane, the acid chloride is added dropwise to 30 ml of dichloroethane at 30°C within 15 minutes and then stirred for 24 hours at 40°C. The suspension is extracted with dichloromethane and water, the organic phase is washed with aqueous acetic acid, dried and the solvent is removed by distillation. The product is converted into its hydrochloride. To purify it the precipitated hydrochloride is taken up in water and extracted with diethyl ether. The aqueous phase is made basic and extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and the solvent is distilled off. The crude product is purified by recrystallisation from acetonitrile. Yield: 1.81 g of slightly beige crystals (= 30% of theoretical); melting point: 138°-139°C.

10.3: cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide :
1.81 g (0.005 mol) of the free base 10.2 are reacted analogously to the method in step 7.3. The purification is carried out by recrystallisation from acetonitrile.
Yield: 1.26 g of white crystals (= 56 % of theoretical); melting point: 228-229°C;

Elemental analysis:	calculated:	C (66.09)	H (6.21)	N (3.08)
	found:	C (66.26)	H (6.26)	N (3.11).

Example 11: Cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide:



11.1.: 9-methyl-xanthene-9-carboxylic acid:

a) methyl 9-methyl-xanthene-9-carboxylate:

Starting from 9.61 g (0.04 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 9.1.a) the reaction to obtain the title compound is carried out analogously to the method in step 10.1.a. Yield: 6.05 g of white crystals (= 60% of theoretical); melting point: 91-92°C.

b) 9-methyl-xanthene-9-carboxylic acid:

Starting from 20.34 g (0.08 mol) of methyl 9-methyl-xanthene-9-carboxylate the reaction to obtain the title compound is carried out analogously to the method in step 10.1.b. Yield: 14.15 g of white crystals (= 74% of theoretical); melting point: 207-208°C.

11.2 Cyclopropyltropine 9-methyl-xanthene-9-carboxylate:

The acid chloride is prepared from 5.0 g (0.021 mol) of 11.1, 5.53 g (0.042 mol) of oxalyl chloride and 4 drops of dimethylformamide in 50 ml of dichloromethane. 3.06 g (0.02 mol) of cyclopropyltropine and the acid chloride produced above are reacted analogously to the method in step 10.2 to obtain the title compound.

Yield: 1.95 g of slightly beige crystals (= 26 % of theoretical); melting point: 87-88°C.

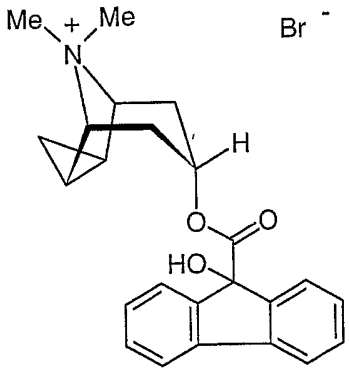
11.3: cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide :

1.95 g (0.005 mol) of the free base 11.1 are reacted analogously to the method in step 7.3. The purification is carried out by recrystallisation from acetonitrile.

Yield: 0.54 g of white crystals (= 23 % of theoretical); melting point: 193-194°C;

Elemental analysis:	calculated:	C (63.83)	H (6.00)	N (2.98)
	found:	C (61.42)	H (6.24)	N (2.97).

Example 12: Cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide :



12.1: methyl 9-hydroxy-fluorene-9-carboxylate:

50.4 g (0.223 mol) of 9-hydroxy-9-fluorenecarboxylic acid are dissolved in 500 ml of methanol, combined with 5 ml (0.089 mol) of conc. sulphuric acid and refluxed for 1 hour. After cooling 100 ml of sodium hydrogen carbonate solution (approx. pH 8) are added and the methanol is largely evaporated down. It is extracted with dichloromethane and water, the organic phase is dried and evaporated to dryness. The purification is carried out by recrystallisation from ethyl acetate.

Yield: 50.0g of white crystals (= 93% of theoretical).

12.2: Cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate:

6.0 g (0.025 mol) of 12.1, 3.45 g (0.023 mol) of cyclopropyltropine and 0.03 g of sodium are reacted analogously to step 7.2. The purification is carried out by recrystallisation from acetonitrile. Yield: 3.46 g of white crystals (= 38 % of theoretical); melting point: 131-132°C.

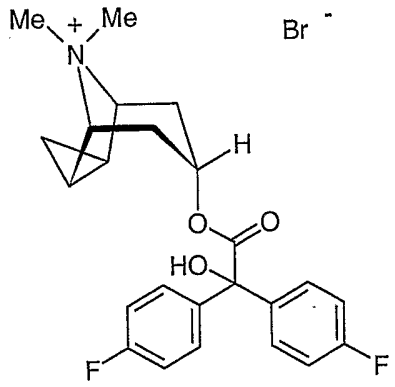
12.3: Cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide :

3.36 g (0.009 mol) of the free base 12.2 are reacted analogously to the method in step 7.3. The purification is carried out by recrystallisation from isopropanol.

Yield: 3.32 g of white crystals (= 79 % of theoretical); melting point: 219-220°C;

Elemental analysis:	calculated:	C (63.16)	H (5.74)	N (3.07)
	found:	C (62.93)	H (5.93)	N (3.10).

Example 13: Cyclopropyltropine 4,4'-difluoromethyl benzilate methobromide :



13.1.: 4,4'-difluoromethyl benzilate:

a) 4,4'-difluorobenzilic acid:

A solution of 24.62 g (0.1 mol) of 4,4'-difluorobenzil in 250 ml dioxane is added dropwise to a solution of 49.99 g (1.25 mol) of NaOH flakes in 300 ml of water at about 100°C and stirred for 2 h. The dioxane is largely distilled off and the aqueous solution remaining is extracted with dichloromethane. When the aqueous solution is acidified with sulphuric acid a precipitate is deposited, which is suction filtered, washed and dried. The filtrate is extracted with dichloromethane, the organic phase is dried over Na_2SO_4 and evaporated to dryness. Yield: 25.01 g (= 95 % of theoretical); melting point: 133°-136°C

b) 4,4'-difluoromethyl benzilate:

25.0 g (0.095 mol) of 4,4'-difluorobenzilic acid are added to freshly prepared sodium ethoxide solution from 2.17 g (0.095 mol) of sodium and 200 ml of ethanol at 20°C and stirred for 3 h. The solution is evaporated to dryness, the residue is dissolved in DMF, 22.57 g (0.16 mol) of methyl iodide are added dropwise at 20°C and the mixture is stirred for 24 h. 300 ml of water are added dropwise to the suspension formed, while cooling with ice, the mixture is extracted with diethyl ether, the organic phase is washed with water, dried over Na_2SO_4 and evaporated to dryness.

Yield: 21.06 g (= 80 % of theoretical).

13.2: cyclopropyltropine 4,4'-difluoromethyl benzilate:

6.2 g (0.022 mol) of 13.1, 3.37 g (0.022 mol) of cyclopropyltropine and 0.051 g sodium are reacted analogously to step 7.2 to obtain the product. The purification is carried out by recrystallisation from acetonitrile.

Yield: 4.15 g of white crystals (= 47 % of theoretical); melting point: 120-121°C.

13.3: cyclopropyltropine 4,4'-difluoromethyl benzilate methobromide :

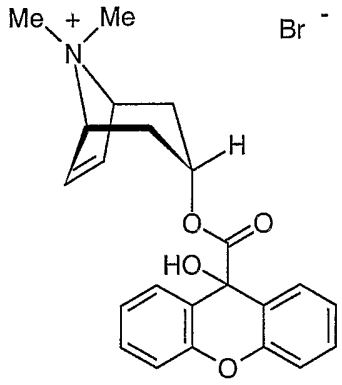
2.0 g (0.005 mol) of the free base 13.2 are reacted analogously to the method in step 7.3. The purification is carried out by recrystallisation from ethanol/diethyl ether.

Yield: 1.8 g of white crystals (= 73 % of theoretical); melting point: 206-207°C;

Elemental analysis:	calculated:	C (58.31)	H (5.30)	N (2.83)
	found:	C (58.15)	H (5.42)	N (2.84).

III) Examples and preparation of the compounds of formula 1g:

Example 14: tropenol 9-hydroxy-xanthene-9-carboxylate methobromide :



14.1.: methyl 9-hydroxy-xanthene-9-carboxylate:

a) methyl xanthene-9-carboxylate :

A sodium ethoxide solution is prepared from 21.75 g (0.95 mol) of sodium and 1500 ml of ethanol. 214 g (0.95 mol) of xanthene-9-carboxylic acid is added batchwise to this solution and the suspension obtained is stirred for 1 hour at ambient temperature. Then the solid is separated off, washed with 1500 ml diethyl ether, the isolated crystals are suspended in 1500 ml of dimethylformamide and combined with 126.73 ml (2.0 mol) of methyl iodide with stirring. The solution formed is left to stand for 24 hours at ambient temperature, then diluted with water to a total volume of 6 l, crystallised, suction filtered, washed with water and dried. Yield: 167 g of white crystals 7 (= 74% of theory)

Melting point: 82° C.

b) methyl 9-hydroxy-xanthene-9-carboxylate:

48.05 g (0.2 mol) methyl xanthene-9-carboxylate are dissolved in 1200 ml of tetrahydrofuran and at 0° C combined with 23.63 g (0.2 mol) of potassium tert. butoxide. Oxygen is the piped in for 2 hours at –10° to –5° C, then the mixture is acidified with 2 N aqueous hydrochloric acid and the majority of the solvent is distilled off. The residue remaining is extracted with ethyl acetate and water, the organic phase is extracted with aqueous $Na_2S_2O_5$ solution, washed with water and dried and the solvent is distilled off. The product is purified by crystallisation from diisopropylether and cyclohexane. Yield: 11.10 g white crystals (= 22% of theory)

14.2: tropenol 9-hydroxy-xanthene-9-carboxylate:

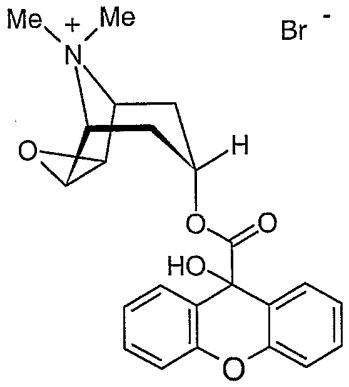
13.65 g (0.053 mol) of methylester 14.1, 8.35 g (0.06 mol) of tropenol and 0.2 g of sodium are heated as a melt at 75 mbar for 4 h over a bath of boiling water with occasional agitation. After cooling the sodium residues are dissolved with acetonitrile, the solution is evaporated to dryness and the residue is extracted with dichloromethane/water. The organic phase is washed with water, dried over $MgSO_4$ and the solvent is distilled off. The product is purified by recrystallisation from diethyl ether/petroleum ether.
Yield: 5.28 g of white crystals (= 27 % of theory); Melting point:117°C.

14.3: tropenol 9-hydroxy-xanthene-9-carboxylate -methobromide :

0.8 g (0.002 mol) of 14.2 are taken up in 20 ml dichloromethane and 20 ml acetonitrile and combined with 1.14 g (0.006 mol) of 50% methylbromide solution in acetonitrile. The reaction mixture is left to stand for 3 days at ambient temperature, during which time the product crystallises. The crystals precipitated are separated off and recrystallised from acetone to purify them.
Yield: 0.94 g of white crystals (= 93 % of theory); Melting point:249-250°C.

Elemental analysis:	calculated:	C (60.27)	H (5.28)	N (3.06)
	found:	C (60.04)	H (5.34)	N (2.98).

Example 15: scopine 9-hydroxy-xanthene-9-carboxylate methobromide :



15.1: scopine 9-hydroxy-xanthene-9-carboxylate:

6.8 g (0.019 mol) tropenolester 14.2 are suspended in 75 ml of dimethylformamide and combined with 0.36 g (0.002 mol) of vanadium-(V)-oxide. At 60°C a solution of 3.52 g (0.037 mol) of H_2O_2-urea in 15 ml of water is added dropwise and the mixture is stirred for 6 hours at 60°C. After cooling to 20°C the mixture is adjusted to pH 2 with 4 N hydrochloric acid and combined with $Na_2S_2O_5$ dissolved in water. The resulting solution is evaporated to dryness, the residue is extracted with dichloromethane/water. The acidic aqueous phase obtained is made basic with Na_2CO_3, extracted with dichloromethane and the organic phase is dried over Na_2SO_4 and concentrated.

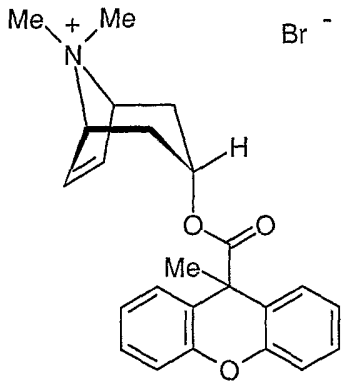
Then 1 ml of acetylchloride are added at ambient temperature and the mixture is stirred for 1 hour. After extraction with 1 N hydrochloric acid the aqueous phase is made basic, extracted with dichloromethane, the organic phase is washed with water and dried over $MgSO_4$. Finally, the solvent is distilled off. The crude product is purified by recrystallisation from diethyl ether. Yield: 5.7 g of yellow oil (= 79 % of theory).

15.2: scopine 9-hydroxy-xanthene-9-carboxylate methobromide :

4.0 g (0.011 mol) of 15.1 are taken up in 60 ml acetonitrile and reacted with 6.27 g (0.033 mol) of 50% methyl bromide solution in acetonitrile analogously to step 14.3. Yield: 3.6 g of white crystals (= 69 % of theory); Melting point:226-227°C.

Elemental analysis: calculated: C (58.24) H (5.10) N (2.95)
found: C (58.33) H (4.98) N (3.05).

Example 16: tropenol 9-methyl-xanthene-9-carboxylate methobromide :



16.1.: 9-methyl-xanthene-9-carboxylic acid:

a) methyl 9-methyl-xanthene-9-carboxylate :

9.61 g (0.04 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 14.1.a) are dissolved in 150 ml of tetrahydrofuran, combined with a solution of 5.0 g (0.042 mol) potassium tert. butoxide in THF and stirred for 10 minutes. 5 ml (0.08 mol) of methyl iodide are then added dropwise with gentle cooling and after all has been added the mixture is stirred for 1 hour at ambient temperature. The reaction mixture is diluted with water to a total volume of 800 ml, extracted with diethyl ether, the organic phase is extracted with saturated, aqueous Na_2CO_3 solution, washed with water, dried over $MgSO_4$ and the solvent is distilled off. The product is purified by recrystallisation from methanol. Yield: 6.05 g of white crystals (= 70% of theory); Melting point:91°-92°C.

b) 9-methyl-xanthene-9-carboxylic acid:

20.34 g (0.08 mol) of the methyl ester described above and 80 ml of 2 molar aqueous sodium hydroxide solution are stirred in 200 ml dioxane for 24 hours at ambient temperature, then the dioxane is distilled off, the mixture is made up to a total volume of 600 ml with water, extracted with diethyl ether and the aqueous phase is acidified with 4 N hydrochloric acid. The product crystallises, is suction filtered and washed with water. It is purified by recrystallisation from acetonitrile. Yield: 14.15 g of white crystals (= 74% of theory); Melting point:207-208°C.

16.2: tropenol 9-methyl-xanthene-9-carboxylate:

From 7.76 g (0.03 mol) of 16.1, 0.06 mol of oxalyl chloride and 4 drops of dimethylformamide the acid chloride is prepared in 100 ml dichloromethane. It is added dropwise as a solution in dichloromethane to 8.77 g (0.063 mol) of tropenol in 140 ml of

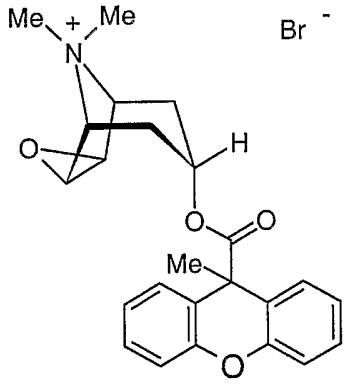
dichloromethane, then stirred for 24 hours at 40°C and cooled. The reaction mixture is extracted with water, dried over $MgSO_4$, and filtered off. The filtrate obtained is acidified to pH2 with ethereal hydrochloric acid, extracted with diethyl ether and the aqueous phase is made basic. After extraction with dichloromethane the organic phase is washed neutral with water, dried over $MgSO_4$ and evaporated to dryness. The residue is dissolved in diethyl ether, insoluble matter is filtered off and the solvent is removed by distillation. Yield: 3.65 g of yellow oil (= 34% of theory).

16.3: tropenol 9-methyl-xanthene-9-carboxylate methobromide :

1.65 g (0.005 mol) of 16.2 are taken up in 20 ml acetonitrile and reacted with 2.85 g (0.015 mol) of 50% methyl bromide solution in acetonitrile analogously to step 14.3. Yield: 1.5 g of white crystals (= 65 % of theory); Melting point:212-213°C.

Elemental analysis: calculated: C (63.16) H (5.74) N (3.07)
found: C (62.50) H (5.94) N (3.11).

Example 17: scopine 9-methyl-xanthene-9-carboxylate methobromide



17.1: scopine 9-methyl-xanthene-9-carboxylate:

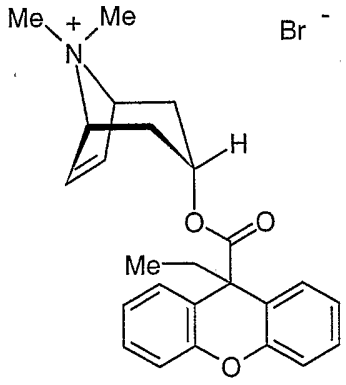
1.9 g (0.005 mol) of tropenol ester 16.2 are suspended in 30 ml of dimethylformamide and reacted with 0.12 g (0.001 mol) of vanadium-(V)-oxide and 0.01 mol of H_2O_2-urea in water analogously to the method according to step 15.1.
Yield: 1.4 g of white crystals (= 74 % of theory).

17.2: scopine 9-methyl-xanthene-9-carboxylate methobromide :

1.35 g (0.004 mol) of 17.1 are taken up in 10 ml of dichloromethane and 20 ml of acetonitrile and reacted with 2.28 g (0.012 mol) of 50% methyl bromide solution in acetonitrile analogously to step 14.3.

Yield: 1.35 g of white crystals (= 71 % of theory); Melting point:208-209°C.
Elemental analysis: calculated: C (61.02) H (5.55) N (2.97)
found: C (59.78) H (5.70) N (2.96).

Example 18: tropenol 9-ethyl-xanthene-9-carboxylate methobromide :



18.1.: 9-ethyl-xanthene-9-carboxylic acid:.

a) methyl 9-ethyl-xanthene-9-carboxylate:

10.0 g (0.042 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 14.1.a) are dissolved in 100 ml of tetrahydrofuran and combined batchwise with 5.16 g (0.044 mol) of potassium tert. butoxide while cooling. Then at about 18-22°C 6.296 ml (0.083 mol) of bromoethane are added dropwise and after it has all been added the mixture is stirred for about 1.5 hours at ambient temperature. The precipitate formed is suction filtered and the solvent is removed by distillation. The residue remaining is taken up in diethyl ether and extracted with water. The organic phase is dried over $MgSO_4$ and the solvent is removed by distillation. The crude product obtained is used in the next step without any further purification.

Yield: 7.92 g of yellow oil. (= 70% of theory).

b) 9-ethyl-xanthene-9-carboxylic acid:

7.92 g (0.03 mol) of the ethyl ester described above and 29.5 ml of 2 molar aqueous sodium hydroxide solution are refluxed in 80 ml dioxane for 2.5 hours. The mixture is worked up as in step 3.1.b).

Yield: 4.46 g of white crystals (= 58% of theory); Melting point:175-176°C.

18.2: tropenol 9-ethyl-xanthene-9-carboxylate:

From 4.46 g (0.03 mol) of 18.1, 4.45 g (0.035 mol) of oxalyl chloride and 3 drops of dimethylformamide the acid chloride is prepared in 40 ml of dichloromethane. It is added as a solution in dichloromethane to 4.87 g (0.035 mol) of tropenol in 60 ml of dichloromethane and reacted analogously to the procedure according to step 16.2 and worked up. Yield: 0.97 g of oil (= 15% of theory).

18.3: tropenol 9-ethyl-xanthene-9-carboxylate methobromide :

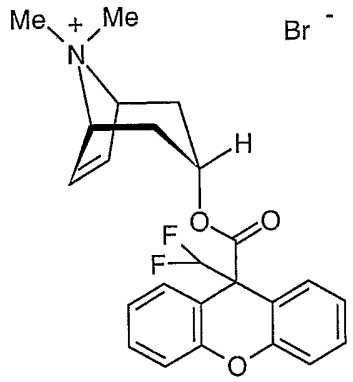
0.97 g (0.003 mol) of 18.2 are taken up in 70 ml acetonitrile and reacted with 1.77 g (0.009 mol) of 50% methyl bromide solution in acetonitrile analogously to Step 14.3. To purify it the product is recrystallised from acetonitrile.

Yield: 0.65 g white crystals (= 46 % of theory); Melting point:217-218°C.

Elemental analysis: calculated: C (63.83) H (6.00) N (2.98)

found: C (61.76) H (6.32) N (2.92).

Example 19: tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide :



19.1.: 9-difluoromethyl-xanthene-9-carboxylic acid:

a) methyl 9-difluoromethyl-xanthene-9-carboxylate :

16.8 g (0.07 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 14.1.a) are dissolved in 300 ml of tetrahydrofuran and 9.1 g (0.077 mol) of potassium tert. butoxide are added batchwise while cooling. Then difluorochloromethane is piped in at 0°C over a period of 1.5 hours. After all the gas has been piped in the reaction mixture is left to stand for 72 hours at ambient temperature. The reaction mixture is then diluted with water to a total volume of about 2000 ml, extracted with ethyl acetate, the organic phase is separated off and washed with 5% aqueous sodium carbonate solution. After being extracted again with water the organic phase is dried over $MgSO_4$ and the solvent is

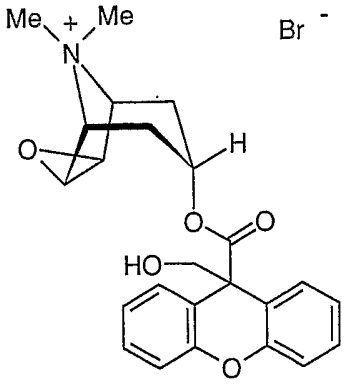
removed by distillation. The crude product is purified by chromatography on silica gel (eluant: cyclohexane/ethyl acetate 98:2) or by recrystallisation from cyclohexane.
Yield: 5.35 g of white crystals (= 26% of theory); Melting point:101°C.

b) 9-difluoromethyl-xanthene-9-carboxylic acid:
5.38 g (0.019 mol) of the ester described above and 18.5 ml of 2 molar aqueous sodium hydroxide solution are reacted in 60 ml of dioxane and worked up analogously to the reaction in Step 16.1.b).
Yield: 2.77 g white crystals (= 53% of theory); Melting point:181-182°C.

19.2: 9-difluoromethyl-xanthene-9-carboxylate tropenol:
From 2.77 g (0.01 mol) of 19.1, 1 ml of oxalyl chloride and 1 drop of dimethylformamide the acid chloride is prepared. It is added to 2.78 g (0.02 mol) of tropenol in 50 ml of 1,2-dichloroethane and reacted and worked up analogously to step 16.2. Yield: 0.6 g of oil (= 15% of theory).

19.3: tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide :
0.6 g (0.002 mol) 19.2 are taken up in 20 ml acetonitrile and reacted with 1.14 g (0.006 mol) of 50% methyl bromide solution in acetonitrile analogously to step 14.3.
Yield: 0.44 g beige crystals (= 45 % of theory); Melting point:227-228°C.
Elemental analysis: calculated: C (58.55) H (4.91) N (2.84)
found: C (57.19) H (5.11) N (2.86).

Example 20: scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide



20.1.: scopine 9-hydroxymethyl-xanthene-9-carboxylate:

3.63 g (0.010 mol) of scopine xanthene-9-carboxylate, which may be obtained as described in WO 92/16528, are dissolved in 20 ml of dimethylformamide and combined with 0.36 g (0.012 mol) of paraformaldehyde. After the addition of 0.168 g (0.002 mol) of potassium tert. butoxide at 20°C the mixture is stirred for 2 hours at ambient temperature. The mixture is acidified to pH 2 with 4 N hydrochloric acid with cooling and the solvent is distilled off *in vacuo*. The residue remaining is extracted with diethyl ether and water, the aqueous phase is made basic with 10% sodium carbonate solution and extracted with dichloromethane. The organic phase is separated off and washed with water, dried and the solvent is distilled off *in vacuo*. To purify it the product is recrystallised from acetonitrile. Yield: 1.55 g white crystals (= 36% of theory); Melting point:232°C.

20.2: scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide :

1.15 g (0.003 mol) of 20.1 are taken up in 20 ml acetonitrile and reacted with 1.71 g (0.009 mol) of 50% methyl bromide solution in acetonitrile analogously to step 14.3.

Yield: 1.28 g of white crystals (= 87 % of theory); Melting point:234°C.

Elemental analysis: calculated: C (59.02) H (5.37) N (2.87)

found: C (59.30) H (5.41) N (3.03).

IV) Examples of Formulations

The following examples of formulations, which may be obtained analogously to methods known in the art, serve to illustrate the present invention more fully without restricting it to the contents of these examples.

Inhalable powders:

1)

Ingredients	µg per capsule
tiotropium bromide	10.8
2 (hydrochloride)	27.9
lactose	4961.3
Total	5000

2)

Ingredients	µg per capsule
tiotropium bromide	21.7
2-en (hydrochloride)	9.0
lactose	4969.3
Total	5000

3)

Ingredients	µg per capsule
tiotropium bromide x H_2O	22.5
2-en (hydrochloride)	18.0
lactose	4959.5
Total	5000

4)

Ingredients	µg per capsule
scopine 2,2-diphenylpropionic acid ester methobromide	200
2-en (hydrochloride)	12
Lactose	24788
Total	25000

5)

Ingredients	µg per capsule
scopine 2,2-diphenylpropionic acid ester methobromide	100
2 (hydrochloride)	50
Lactose	12350
Total	12500

6)

Ingredients	µg per capsule
scopine 2,2-diphenylpropionic acid ester methobromide	50
2 (hydrochloride)	50
Lactose	4900
Total	5000

7)

Ingredients	µg per capsule
tropenol 2,2-diphenylpropionic acid ester methobromide	200
2-en (hydrochloride)	24
Lactose	24776
Total	25000

8)

Ingredients	µg per capsule
scopine 3,3',4,4'-tetrafluorobenzilic acid ester methobromide	100
2 (hydrochloride)	50
Lactose	12350
Total	12500

9)

Ingredients	µg per capsule
tropenol 3,3',4,4'-tetrafluorobenzilic acid ester methobromide	100
2 (hydrochloride)	50
Lactose	12350
Total	12500

10)

Ingredients	µg per capsule
scopine 4,4'-tetrafluorobenzilic acid ester methobromide	100
2 (hydrochloride)	50
Lactose	12350
Total	12500

11)

Ingredients	µg per capsule
tropenol 4,4'-tetrafluorobenzilic acid ester methobromide	100
2 (hydrochloride)	50
Lactose	12350
Total	12500

12)

Ingredients	µg per capsule
1a-en (bromide)	150
2 (hydrochloride)	50
Lactose	12300
Total	12500

13)

Ingredients	µg per capsule
1a-en (bromide)	150
2-en (hydrochloride)	50
Lactose	12300
Total	12500

14)

Ingredients	µg per capsule
1a-en (bromide)	150
2-en (hydrochloride)	15
Lactose	12335
Total	12500

15)

Ingredients	µg per capsule
1a-en (bromide)	200
2 (hydrochloride)	50
Lactose	24750
Total	25000

16)

Ingredients	µg per capsule
example 6	80
2-en (hydrochloride)	12
Lactose	12408
Total	12500

17)

Ingredients	µg per capsule
example 6	30
2 (hydrochloride)	50
Lactose	12420
Total	12500

18)

Ingredients	µg per capsule
example 9	80
2 (hydrochloride)	50
Lactose	12370
Total	12500

19)

Ingredients	µg per capsule
example 6	100
2-en (hydrochloride)	25
Lactose	24875
Total	25000

20)

Ingredients	µg per capsule
example 6	24
2-en (hydrochloride)	12
Lactose	4964
Total	5000

B) Propellant-containing inhalable aerosols:

1)

Ingredients	% by weight
example 6	0.010
2 (hydrochloride)	0.066
Soya lecithin	0.2
TG 134a : TG 227 = 2:3	ad 100

2)

Ingredients	% by weight
example 6	0.030
2-en (hydrochloride)	0.033
Absolute ethanol	0.5
Isopropyl myristate	0.1
TG 227	ad 100

3)

Ingredients	% by weight
example 6	0.010
2-en (hydrochloride)	0.035
Soya lecithin	0.2
TG 134a : TG 227 = 2:3	ad 100

4)

Ingredients	% by weight
tiotropium bromide	0.015
2 (hydrochloride)	0.066
soya lecithin	0.2
TG 134a : TG 227 = 2:3	ad 100

5) 5)

Ingredients	% by weight
tiotropium bromide	0.029
2-en (hydrochloride)	0.033
absolute ethanol	0.5
isopropyl myristate	0.1
TG 227	ad 100

6)

Ingredients	% by weight
tiotropium bromide	0.042
2 (hydrochloride)	0.047
absolute ethanol	30
purified water	1.5
anhydrous citric acid	0.002
TG 134a	ad 100

7)

Ingredients	% by weight
scopine 2,2-diphenylpropionic acid ester methobromide	0.020
2 (hydrochloride)	0.066
Soya lecithin	0.2
TG 11 : TG12 = 2:3	ad 100

8)

Ingredients	% by weight
scopine 2,2-diphenylpropionic acid ester methobromide	0.039
2-en (hydrochloride)	0.033
Absolute ethanol	0.5
Isopropyl myristate	0.1
TG 227	ad 100

9)

Ingredients	% by weight
tropenol 2,2-diphenylpropionic acid ester methobromide	0.020
2 (hydrochloride)	0.066
Soya lecithin	0.2
TG 11 : TG12 = 2:3	ad 100

10)

Ingredients	% by weight
tropenol 2,2-diphenylpropionic acid ester methobromide	0.039
2-en (hydrochloride)	0.033
Absolute ethanol	0.5
Isopropyl myristate	0.1
TG 227	ad 100

11)

Ingredients	% by weight
1a-en (bromide)	0.050
2 (hydrochloride)	0.066
Soya lecithin	0.2
TG 134a : TG 227 = 2:3	ad 100

12)

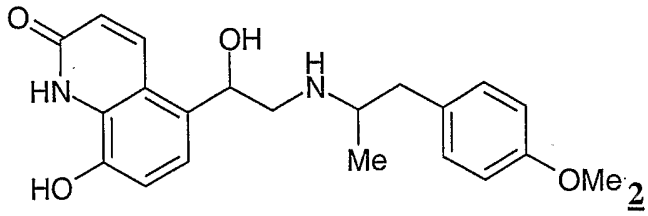
Ingredients	% by weight
1a-en (bromide)	0.080
2-en (hydrochloride)	0.033
Absolute ethanol	0.5
Isopropyl myristate	0.1
TG 227	ad 100

13)

Ingredients	% by weight
1a-en (bromide)	0.050
2-en (hydrochloride)	0.035
Soya lecithin	0.2
TG 134a : TG 227 = 2:3	ad 100

Patent Claims

1) Pharmaceutical compositions, comprising one or more, preferably one anticholinergic 1 and a betamimetic of formula 2

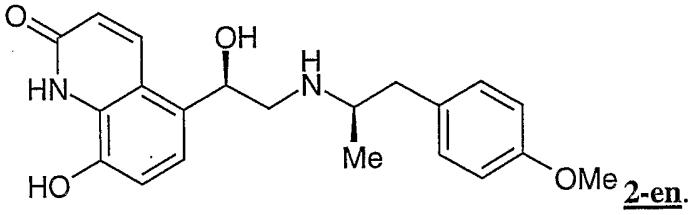


2

optionally in the form of its diasteromers, mixtures of its diasteromers, racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof and optionally together with a pharmaceutically acceptable excipient.

2) Pharmaceutical composition according to claim 1, characterised in that the active substances 1 and 2 are present either together in a single formulation or in two separate formulations.

3) Pharmaceutical composition according to claim 1 or 2, characterised in that 2 is present in form of its enantiomer of formula **2-en**



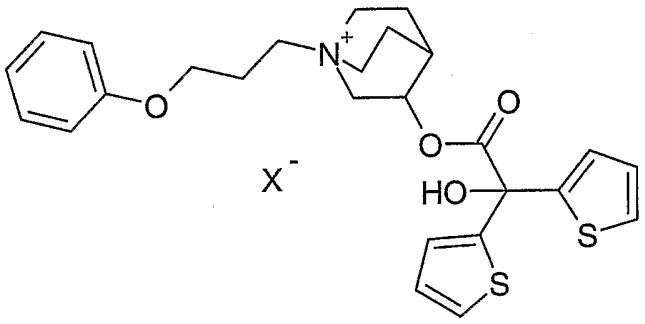
2-en.

4) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that 1 is selected from among tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts or trospium salts, optionally in the form of its diasteromers, mixtures of its diasteromers, racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof.

5) Pharmaceutical composition according to claim 4, characterised in that the salts **1** contain as counter-ion (anion), chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate.

6) Pharmaceutical composition according to claim 4 or 5, characterised in that the salts **1** are selected from among tiotropium bromide, oxitropium bromide and ipratropium bromide.

7) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is a salt of formula **1a**



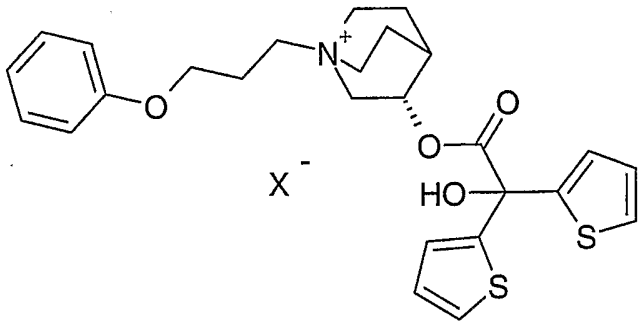
1a

wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

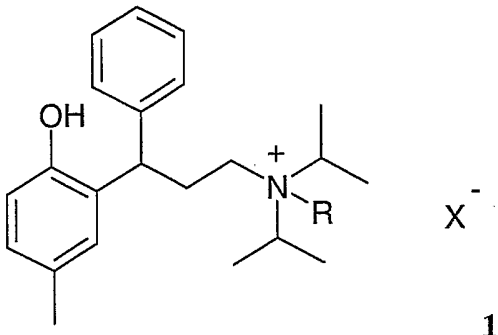
optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

8) Pharmaceutical composition according to claim 7, characterised in that **1** is present in form of the enantiomer formula **1a-en**



1a-en.

9) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is a compound of formula **1b**



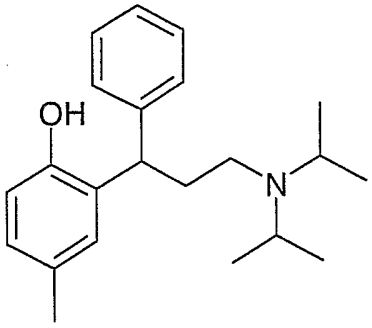
1b

wherein R is either methyl or ethyl and wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

10) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is a compound of formula **1b-base**

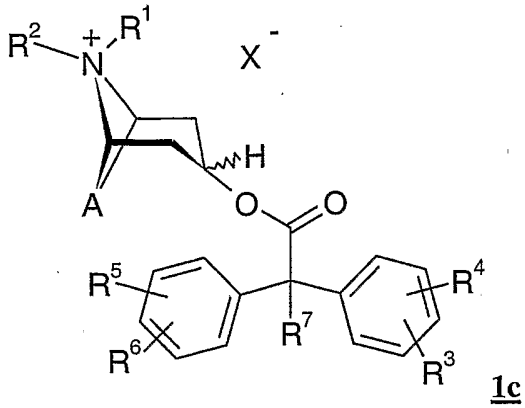


1b-base

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

11) Pharmaceutical composition according to claim 9 or 10, characterised in that **1b** or **1b-base** are present in form of its R-enantiomer.

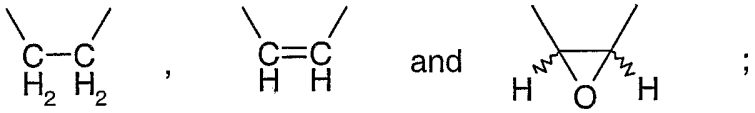
12) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is present in form of a compound of formula **1c**



1c

wherein

A denotes a double-bonded group selected from among



;

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

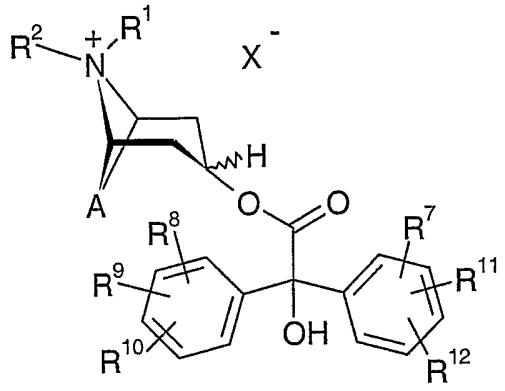
R^1 and R^2 which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

R^3, R^4, R^5 and R^6, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2;

R^7 denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, $-CH_2-F$, $-CH_2-CH_2-F$, $-O-CH_2-F$, $-O-CH_2-CH_2-F$, $-CH_2-OH$, $-CH_2-CH_2-OH$, CF_3, $-CH_2-OMe$, $-CH_2-CH_2-OMe$, $-CH_2-OEt$, $-CH_2-CH_2-OEt$, -O-COMe, -O-COEt, $-O-COCF_3$, $-O-COCF_3$, fluorine, chlorine or bromine,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

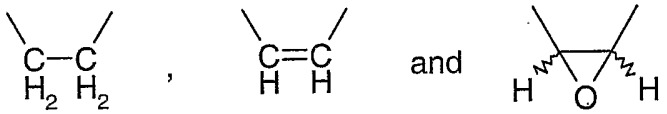
13) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is present in form of a compound of formula **1d**



1d

wherein

A denotes a double-bonded group selected from among



;

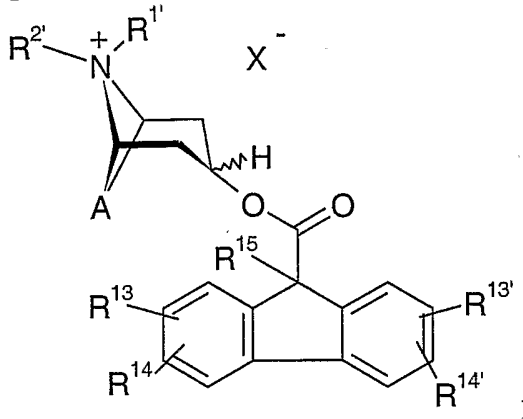
X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

R^1 and R^2 which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

R^7, R^8, R^9, R^{10}, R^{11} and R^{12}, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2, with the proviso that at least one of the groups R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is not hydrogen,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

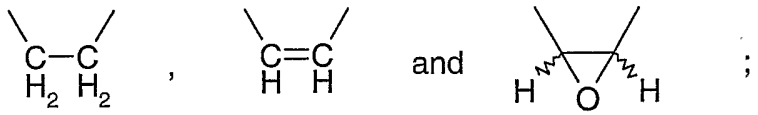
14) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is present in form of a compound of formula **1e**



1e

wherein

A denotes a double-bonded group selected from among



;

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

R^{15} denotes hydrogen, hydroxy, methyl, ethyl, $-CF_3$, CHF_2 or fluorine;

$R^{1'}$ and $R^{2'}$ which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen,

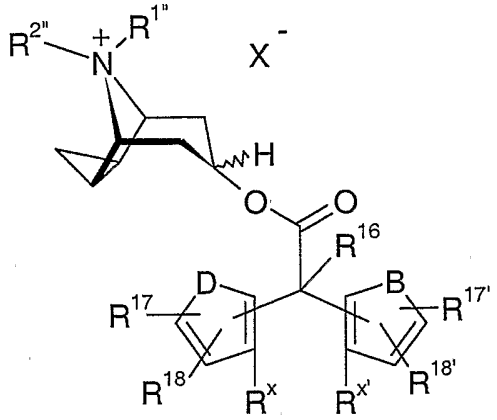
or

$R^{1'}$ and $R^{2'}$ together denote a $-C_3$-C_5-alkylene-bridge;

R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

15) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is present in form of a compound of formula **1f**



1f

wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

D and B which may be identical or different, preferably identical, denote -O, -S, -NH, $-CH_2$, -CH=CH, or $-N(C_1\text{-}C_4\text{-alkyl})$-;

R^{16} denotes hydrogen, hydroxy, $-C_1\text{-}C_4$-alkyl, $-C_1\text{-}C_4$-alkyloxy, $-C_1\text{-}C_4$-alkylene-Halogen, -O-$C_1\text{-}C_4$-alkylene-halogen, $-C_1\text{-}C_4$-alkylene-OH, $-CF_3$, CHF_2, $-C_1\text{-}C_4$-alkylene-$C_1\text{-}C_4$-alkyloxy, -O-$COC_1\text{-}C_4$-alkyl, -O-$COC_1\text{-}C_4$-alkylene-halogen, $-C_1\text{-}C_4$-alkylene-$C_3\text{-}C_6$-cycloalkyl, -O-$COCF_3$ or halogen;

$R^{1"}$ and $R^{2"}$ which may be identical or different, denote $-C_1\text{-}C_5$-alkyl, which may optionally be substituted by $-C_3\text{-}C_6$-cycloalkyl, hydroxy or halogen,

or

$R^{1"}$ and $R^{2"}$ together denote a $-C_3\text{-}C_5$-alkylene bridge;

R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$, which may be identical or different, denote hydrogen, $C_1\text{-}C_4$-alkyl, $C_1\text{-}C_4$-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen;

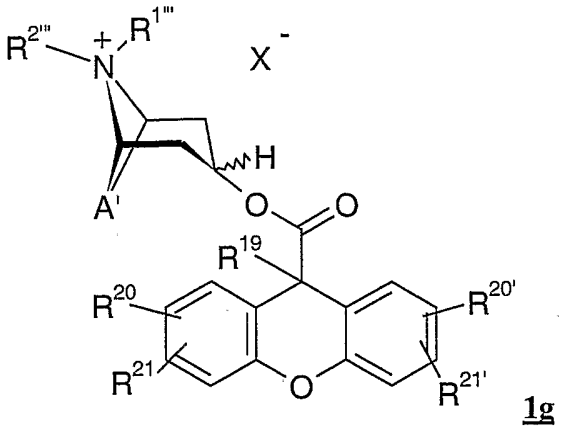
R^X and $R^{X'}$ which may be identical or different, denote hydrogen, $C_1\text{-}C_4$-alkyl, $C_1\text{-}C_4$-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen

or

R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH, $-CH_2$, $-CH_2\text{-}CH_2$-, $-N(C_1\text{-}C_4\text{-alkyl})$, $-CH(C_1\text{-}C_4\text{-alkyl})$- and $-C(C_1\text{-}C_4\text{-alkyl})_2$,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

16) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that **1** is present in form of a compound of formula **1g**

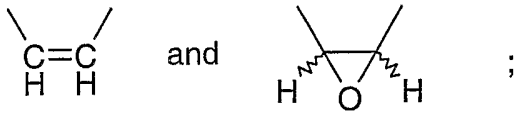


1g

wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

A' denotes a double-bonded group selected from among



;

R^{19} denotes hydroxy, methyl, hydroxymethyl, ethyl, $-CF_3$, CHF_2 or fluorine;

$R^{1'''}$ and $R^{2'''}$ which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen,

or

$R^{1'''}$ and $R^{2'''}$ together denote a $-C_3$-C_5-alkylene-bridge;

R^{20}, R^{21}, $R^{20'}$ and $R^{21'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

17) Pharmaceutical compositions according to one of claims 1 to 16, characterised in that the weight ratios of **1** and **2** are generally in the range from 1:400 to 150:1, preferably in the range from 1: 350 to 100:1.

18) Pharmaceutical composition according to one of claims 1 to 17, characterised in that it is in the form of a preparation suitable for inhalation.

19) Pharmaceutical composition according to claim 18, characterised in that it is a preparation selected from among the inhalable powders, propellant-containing metered-dose aerosols and propellant-free inhalable solutions.

20) Pharmaceutical composition according to claim 19, characterised in that it is an inhalable powder which contains **1** and **2** in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.

21) Inhalable powder according to claim 20, characterised in that the excipient has a maximum average particle size of up to 250µm, preferably between 10 and 150µm.

22) Pharmaceutical composition according to claim 19, characterised in that it is an inhalable powder which contains only the active substances **1** and **2** as its ingredients.

23) Pharmaceutical composition according to claim 19, characterised in that it is a propellant-containing inhalable aerosol which contains **1** and **2** in dissolved or dispersed form.

24) Propellant-containing inhalable aerosol according to claim 23, characterised in that it contains, as propellant gas, hydrocarbons such as n-propane, n-butane or isobutane or halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

25) Propellant-containing inhalable aerosol according to claim 24, characterised in that the propellant gas is TG11, TG12, TG134a, TG227 or mixtures thereof, preferably TG134a, TG227 or a mixture thereof.

26) Propellant-containing inhalable aerosol according to one of claims 23 to 25, characterised in that it may contain up to 5 % by weight of active substance **1** and/or **2**.

27) Pharmaceutical composition according to claim 19, characterised in that it is a propellant-free inhalable solution which contains water, ethanol or a mixture of water and ethanol as solvent.

28) Inhalable solution according to claim 27, characterised in that it optionally contains other co-solvents and/or excipients.

29) Inhalable solution according to claim 28, characterised in that it contains as co-solvents ingredients which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters.

30) Inhalable solutions according to one of claims 28 or 29, characterised in that they contain as excipients surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavourings, pharmacologically acceptable salts and/or vitamins.

31) Inhalable solutions according to claim 30, characterised in that they contain as complexing agents editic acid or a salt of editic acid, preferably sodium edetate.

32) Use of a composition according to one of claims 1 to 31 for preparing a medicament for the treatment of inflammatory or obstructive respiratory complaints, particularly asthma or COPD.

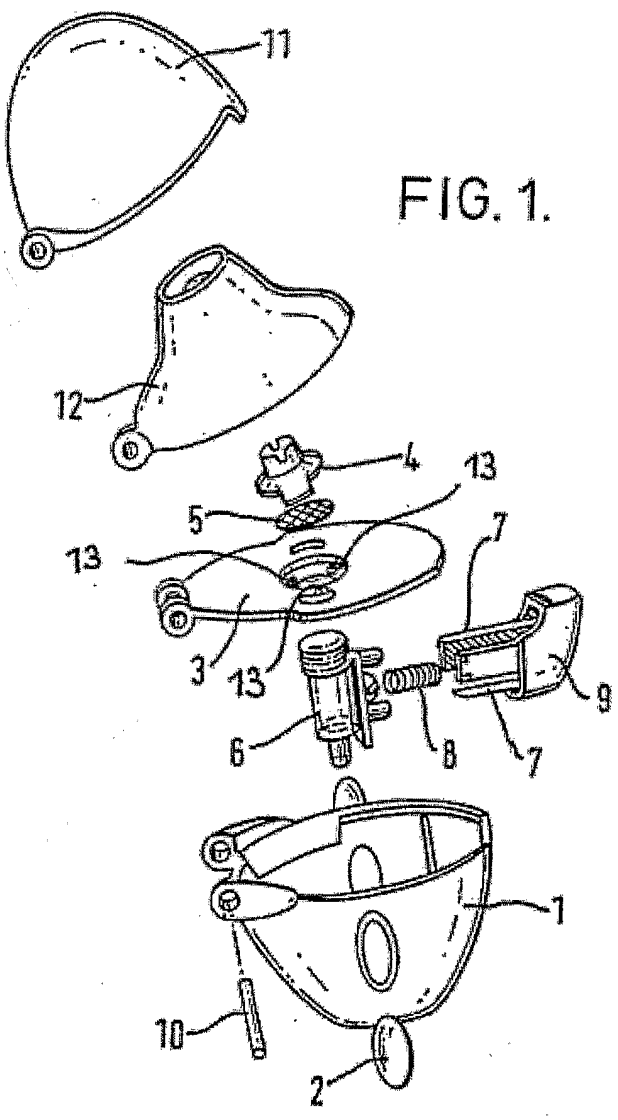


FIG. 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008013

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4704 A61K31/46 A61K31/137 A61K31/439 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 1 157 689 A (CHIESI FARMA SPA) 28 November 2001 (2001-11-28) paragraphs '0035!, '0036!; claim 2	1-6, 17-32 7-16
Y	CALVO G M ET AL: "IS IT USEFUL TO ADD AN ANTICHOLINERGIC TREATMENT TO BETA2-ADRENERGIC MEDICATION IN ACUTE ASTHMA ATTACK" JOURNAL OF INVESTIGATIONAL ALLERGOLOGY AND CLINICAL IMMUNOLOGY, BARCELONA, ES, vol. 8, no. 1, January 1998 (1998-01), pages 30-34, XP009018610 ISSN: 1018-9068 see introduction	1-32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2004	25/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allnutt, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/151597 A1 (BANERJEE PARTHA S ET AL) 17 October 2002 (2002-10-17) page 8, column 1, line 39, paragraphs 76,80	1-8, 17-32
Y	WO 01/04118 A (ALMIRALL PRODESFARMA SA ; BUIL ALBERO MARIA ANTONIA (ES); FERNANDEZ FO) 18 January 2001 (2001-01-18) page 1, lines 11-20; claims 20,34; examples 44,85	1-3,5-8, 17-32
Y	EP 0 147 719 A (TANABE SEIYAKU CO) 10 July 1985 (1985-07-10) page 1, lines 5-11	1-32
Y	WO 02/32899 A (BOEHRINGER INGELHEIM PHARMA ; PIEPER MICHAEL PAUL (DE); POHL GERALD (D) 25 April 2002 (2002-04-25) cited in the application page 28, lines 8-12; claim 10 page 29, lines 34,35	1-3,5,6, 12,17-32
Y	WO 02/32898 A (BOEHRINGER INGELHEIM PHARMA ; PIEPER MICHAEL PAUL (DE); POHL GERALD (D) 25 April 2002 (2002-04-25) cited in the application see claims page 50, lines 11-15; claim 11	1-3,5,6, 13,17-32
A	EP 1 258 253 A (ASAHI CHEMICAL IND) 20 November 2002 (2002-11-20) claims 3,4	1-3,5,6, 9-11, 17-32
Y	IZEBOUD C A ET AL: "Stereoselectivity at the beta2-adrenoceptor on macrophages is a major determinant of the anti-inflammatory effects of beta2-agonists" NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 362, no. 2, August 2000 (2000-08), pages 184-189, XP002300185 ISSN: 0028-1298 abstract	3
E	EP 1 452 179 A (CHIESI FARMA SPA) 1 September 2004 (2004-09-01) paragraph '0033!; claims 1,2,10,14,15	1-6, 17-32
P,X	WO 03/074025 A (BRAMBILLA GAETANO ; CHURCH TANYA KATHLEEN (IT); FERRARIS ALESSANDRA (I) 12 September 2003 (2003-09-12) claims 2,4,5,18 page 11, line 18 - line 22	1-6, 17-32

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008013

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 03/064419 A (BOEHRINGER INGELHEIM PHARMA ; PESTEL SABINE (DE); POHL GERALD (DE); SP) 7 August 2003 (2003-08-07) page 17, lines 1-14; claim 1.10	12-16
P,A	WO 2004/004704 A (BOEHRINGER INGELHEIM PHARMA ; PAIRET MICHEL (DE); MEADE CHRISTOPHER JO) 15 January 2004 (2004-01-15) claim 1	12-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/008013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1157689 A	28-11-2001	WO 0189480 A1	29-11-2001
		EP 1157689 A1	28-11-2001
		NO 20025568 A	20-11-2002
		AU 5070100 A	03-12-2001
		BG 107256 A	30-06-2003
		BR 0015884 A	08-07-2003
		CA 2411047 A1	29-11-2001
		CZ 20023835 A3	16-04-2003
		EE 200200649 A	15-06-2004
		HR 20021025 A2	29-02-2004
		HU 0302007 A2	29-09-2003
		JP 2003534266 T	18-11-2003
		SK 16522002 A3	01-04-2003
		US 2004047809 A1	11-03-2004
		US 2002025299 A1	28-02-2002
US 2002151597 A1	17-10-2002	CA 2438544 A1	24-10-2002
		EP 1381346 A2	21-01-2004
		WO 02083079 A2	24-10-2002
		US 2002151598 A1	17-10-2002
WO 0104118 A	18-01-2001	ES 2165768 A1	16-03-2002
		AT 235492 T	15-04-2003
		AU 6433000 A	30-01-2001
		BG 106301 A	30-08-2002
		BR 0012434 A	02-04-2002
		CA 2381165 A1	18-01-2001
		CN 1373760 T	09-10-2002
		CZ 20020121 A3	13-11-2002
		DE 60001840 D1	30-04-2003
		DE 60001840 T2	11-12-2003
		DK 1200431 T3	21-07-2003
		EE 200200017 A	15-04-2003
		WO 0104118 A2	18-01-2001
		EP 1200431 A2	02-05-2002
		ES 2193098 T3	01-11-2003
		HK 1042487 A1	18-07-2003
		HU 0202100 A2	28-10-2002
		JP 2003504368 T	04-02-2003
		NO 20020180 A	13-03-2002
		PL 357160 A1	12-07-2004
		PT 1200431 T	31-07-2003
		SI 1200431 T1	31-10-2003
		SK 432002 A3	01-04-2003
		TR 200200768 T2	22-07-2002
		US 2003055080 A1	20-03-2003
		US 2004132768 A1	08-07-2004
		ZA 200200232 A	10-04-2003
EP 0147719 A	10-07-1985	AT 44954 T	15-08-1989
		CA 1258859 A1	29-08-1989
		CA 1259074 A2	05-09-1989
		DE 3479119 D1	31-08-1989
		EP 0147719 A2	10-07-1985
		HK 89790 A	09-11-1990
		JP 63054362 A	08-03-1988
		JP 1765229 C	11-06-1993
		JP 4046950 B	31-07-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/008013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0147719 A		JP 60208965 A	21-10-1985
		SG 75290 G	23-11-1990
		US RE33024 E	15-08-1989
		US 4579854 A	01-04-1986
WO 0232899 A	25-04-2002	DE 10050994 A1	18-04-2002
		AT 259805 T	15-03-2004
		AU 1397502 A	29-04-2002
		BG 107688 A	30-09-2003
		BR 0114635 A	10-02-2004
		CA 2425557 A1	11-04-2003
		CN 1468236 T	14-01-2004
		DE 50101524 D1	25-03-2004
		DK 1325001 T3	21-06-2004
		EE 200300151 A	16-06-2003
		WO 0232899 A1	25-04-2002
		EP 1325001 A1	09-07-2003
		EP 1382606 A2	21-01-2004
		HU 0301203 A2	28-10-2003
		JP 2004511557 T	15-04-2004
		NO 20031693 A	28-05-2003
		NZ 525836 A	24-09-2004
		PT 1325001 T	30-07-2004
		SI 1325001 T1	31-08-2004
		SK 4352003 A3	05-08-2003
		US 2004087617 A1	06-05-2004
		US 2002115680 A1	22-08-2002
		ZA 200302914 A	14-11-2003
WO 0232898 A	25-04-2002	DE 10050995 A1	18-04-2002
		AU 1397702 A	29-04-2002
		CA 2425560 A1	11-04-2003
		WO 0232898 A2	25-04-2002
		EP 1328524 A2	23-07-2003
		JP 2004511556 T	15-04-2004
		US 2002119991 A1	29-08-2002
EP 1258253 A	20-11-2002	AU 2710301 A	07-08-2001
		CA 2398199 A1	02-08-2001
		EP 1258253 A1	20-11-2002
		WO 0154728 A1	02-08-2001
		US 2003018061 A1	23-01-2003
EP 1452179 A	01-09-2004	EP 1452179 A1	01-09-2004
		WO 2004075896 A1	10-09-2004
WO 03074025 A	12-09-2003	EP 1340492 A1	03-09-2003
		EP 1415647 A1	06-05-2004
		BR 0303348 A	13-07-2004
		WO 03074023 A1	12-09-2003
		WO 03074024 A1	12-09-2003
		WO 03074025 A2	12-09-2003
		NO 20034874 A	23-12-2003
		WO 2004037227 A1	06-05-2004
WO 03064419 A	07-08-2003	DE 10203741 A1	14-08-2003
		CA 2472149 A1	07-08-2003
		WO 03064419 A1	07-08-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/008013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03064419 A		US 2003199539 A1	23-10-2003
		US 2004157832 A1	12-08-2004
WO 2004004704 A	15-01-2004	DE 10230769 A1	22-01-2004
		WO 2004004704 A1	15-01-2004
		US 2004058950 A1	25-03-2004